

Insulinoma in Ferrets

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“Eat when you can, sleep when you can, and above all, don’t screw with the pancreas...”

Thinking back on everything I learned in vet school, this oft-quoted pearl probably served me best over the years. However, all good things must come to an end, and eventually you hit middle age (*watch what you eat!*), with a burgeoning practice and a houseful of kids (*no more good night’s sleep!*) and start treating ferrets (*and find yourself in the pancreas business!*)

However, I do have two things going for me: 1) most ferrets never heard that quote, and 2) the ferret pancreas is as unique in the animal kingdom as the ferret itself.

The pancreas explained...

The pancreas is an essential organ in the body, as it produces a wide range of substances vital for survival. One part of the pancreas (known as the *exocrine* pancreas) produces digestive enzymes, which, when released into the intestine, break down protein, fat, and starch. Another part (a.k.a. the *endocrine* pancreas) produces hormones (including insulin) that are released into the bloodstream and closely regulate the levels of glucose in the blood and its entry into various tissues, where it is used as fuel.

In the living animal, glucose is one of the most important molecules, only slightly less important than oxygen and water. Glucose (also known as blood sugar), is the primary fuel for the body’s cells, and without it, normal cellular processes cannot be

performed, resulting in dysfunction and ultimately, cellular death.

Cells of the body vary in their sensitivity to diminished levels of blood glucose (“glucose starvation”). Some cells, such as neurons in the brain, are exquisitely sensitive to vacillations in blood glucose, while others, such as muscle cells, are more resistant. As neurons are so sensitive, the earliest and most profound signs of hypoglycemia are generally neurologic in nature,, and symptom severity is proportional to the severity of hypoglycemia. (Hyperglycemia - increased blood sugar - is far less common, and is the result of a total *lack* of insulin in the blood. This condition is known as diabetes mellitus, and is still fairly rare in the ferret - although more commonly diagnosed today than in years past).



Ferrets have more pancreas than any other domestic animal – you’ve got to be patient and thorough when examining it for insulinomas.

Now, what makes the *ferret* pancreas so unique? To start with, ferrets have twice as much pancreas, pound for pound, as any other domestic species. Due to the ferret’s rapid GI transit time (4 hours from “end to end”), the production requirements for the pancreatic’s digestive enzymes are extremely high. Another very distinct difference in the ferret is that unlike the pancreas of most other species (which often tends to break down even with the most gentle handling), the ferret pancreas is much hardier, allowing us to surgically manipulate

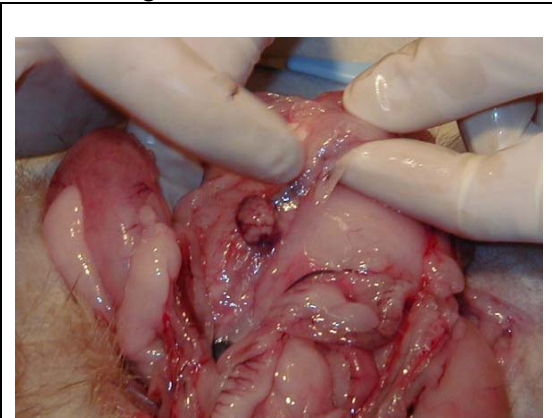
it, isolating and removing tumors with minimal postoperative inflammation.

Insulinoma arising...

Insulinomas result from the uncontrolled growth of the cells of the endocrine pancreas, namely the insulin-secreting beta cells. Neoplastic beta cells pay no heed to the normal feedback mechanisms which regulate blood glucose levels, and secrete insulin whenever they want to, and in whatever amounts they want to. In most affected ferrets, the inappropriate secretion of insulin is initially sporadic, resulting in bouts of hypoglycemia, or lowered blood sugar. Over time, attacks of hypoglycemia become more and more frequent, until hypoglycemia becomes constant.

The frequency of insulinoma increases with age in ferrets, and most clinical (symptom-producing) tumors are identified between the ages of 5 and 7. Other insulinomas are identified during routine exploration of the abdomen for other problems (adrenal disease, foreign bodies, etc.) and perhaps the largest subset of all are found as incidental findings at autopsy, suggesting that many of these tumors do not secrete insulin in any significant amount.

At surgery, insulinomas appear as a single nodule within the pancreas, or in long-standing cases, multiple tumors. When viewed at surgery, they are often firm to the touch, and a different color than the surrounding tissue.



**Large insulinoma on the pancreas of a ferret.
(Photo courtesy West Wales Ferret Welfare)**

Insulinoma unmasked...

Diagnosis of insulinoma is not particularly difficult for the observant owner and veterinarian. In most cases, clinical signs are very characteristic – sporadic loss of contact with surroundings (“trances”), drooling, circling, or difficulty walking are all well-known signs of insulinoma in ferrets. Clinical symptoms may be more subtle (lack of energy, hindlimb weakness) or more profound (vocalization and coma) depending on the current level of blood glucose.

Definitive diagnosis of insulinoma is made in the vast majority of cases by a blood glucose test – rapid, cost-effective, and gloriously simple. In cases in which the glucose level is less than 60 g/dl (normal in the ferret is 80-120 g/dl), the presence of an insulinoma is assured (even without corroborative evidence of clinical signs. If the blood glucose reading is between 60 and 80 g/dl, concomitant clinical signs of hypoglycemia are required to make the diagnosis. In cases in which the glucose level exceeds 80 mg, other forms of neurologic diseases should be investigated as well. Remember that insulin secretion in some tumors is sporadic, and normoglycemia one day may become hypoglycemia the next.

The determination of insulin levels in the blood may be occasionally useful, but are largely unnecessary in most cases. While it may yield additional corroborative evidence of insulinoma, it often adds unnecessary delay to definitive treatment. I tend to reserve this test only for those cases in which hypoglycemia is present without evidence of clinical signs.

Hypoglycemia and neurologic signs are not the exclusive province of insulinoma in the ferret; however, they are far and away the

leading cause of these symptoms. In cases in which hypoglycemia is seen without neurologic dysfunction, other causes should be investigated in addition to insulinoma.

Laboratory error is usually the most common use of spurious hypoglycemia. When blood is drawn from a vein, the red blood cells in the tube will continue to utilize glucose, thereby artificially lowering the measured glucose value. (How are they supposed to know they're not in a vein?). For this reason, all hypoglycemic patients should have their blood glucose test repeated on a separate day with careful attention to laboratory technique. The use of gas anesthesia during the blood draw will not affect the levels of glucose in the sample.

Overwhelming bacterial infections in the blood can also result in hypoglycemia, as bacteria will also use sugar for fuel. However, in these cases, other obvious clinical signs of infection will usually be present, such as a high fever or a wildly aberrant white blood cell count.

The practice of fasting prior to blood glucose test is controversial, especially during initial workup for hypoglycemia. The majority of insulinomic ferrets will exhibit hypoglycemia without fasting, and may be thrown into a crisis situation following a fast..

Insulinoma undone

Both medical and surgical treatment for insulinoma are widely used in the ferret; however surgical options should be explored first, as they: a) rapidly halt clinical signs by removing the aberrant source of insulin, and b) are generally the only possibility of a cure in affected animals. Most ferret owners and vets know, however, the incidence of recurrence of insulinoma after surgery is high, averaging about 40% over a 10 months span. The cause of this high rate of recurrence is not truly known - some vets believe that the formation of multiple tumors over time is the expression of an innate

genetic or metabolic defect in affected animals, while others believe that the formation of new tumors indicates generalized seeding of the pancreas, with subsequent growth of microscopic tumors that were not visible to the naked eye at surgery.

Another significant difference with insulinoma in the ferret, as opposed to dogs and cats, is the fact that the prognosis (or long-term behavior) of this tumor is actually far better. In the dog and cat, this tumor tends to metastasize widely throughout the abdomen, seeding the liver, spleen, and other abdominal organs. In the ferrets, insulinomas are almost always restricted to the pancreas, and although they may recur within the other areas of the pancreas, they are almost never found at distant sites. This makes surgical excision of insulinomas in ferrets far more successful than in other pet species.

Insulinoma surgery is considered one of the most routine surgeries by vets who treat ferrets on a regular basis. Most insulinomas are minimally vascularized, and heavy bleeding is very uncommon. Insulinomas are hard nodules in an otherwise soft organ, often discolored, and can easily and quickly be removed with a few precise strokes of a scalpel blade. Another benefit of surgical treatment is that it gives the vet an opportunity to quickly explore the rest of the abdomen, looking for enlarged adrenals, gastric foreign bodies, and other treatable lesions.

Occasionally, discrete nodules are not perceived by the naked eye; but if hypoglycemia has been documented (and rechecked), the prudent practitioner will not simply sew up the patient. Partial pancreatectomy, or the removal an entire segment of the pancreas, has been shown to be of benefit in such cases. In fact, when partial pancreatectomy was evaluated against simple nodulectomy for treatment of insulinoma, ferrets treated with partial pancreatectomy had disease-free intervals almost twice as long as those with simple

nodulectomy, and ten times longer than those receiving only medical treatment.

I am often asked about the utility of performing surgery for insulinoma in ferrets, and often respond with this analogy. Imagine YOU had a tumor that was preventing you from enjoying the things in life that you like to do. Now imagine that I told you that I could remove that tumor and you would have a 6 in 10 chance of being cured, and if you weren't actually cured, you would likely have an additional six to ten disease-free years. Doesn't that sound like a good deal? If you understand that a month in the life of a ferret is equivalent to one human year, it sounds like a winner to me.

In a small number of cases, the hypoglycemia seen prior to surgery may rapidly change to hyperglycemia, even diabetes. The mechanism behind this reversal of fortune is as follows: When the levels of insulin in the blood are high, beta cells shut down normal production of insulin. If your only job is to produce insulin, and there is no need for it, eventually you will just wither away (or *atrophy*).

This is exactly what happens in some cases of long-standing insulinoma. When the tumor is at long last removed by surgery, the remaining normal islets have atrophied from disuse, and insulin production is markedly diminished. The duration of hyperglycemia is directly proportional to the atrophy of the normal islet cells; luckily, post-surgical hyperglycemia is transient in most cases, and specific treatment is unnecessary. However, in the rare case, permanent damage from long-standing tumors may lead to diabetes mellitus (another good reason for prompt surgical intervention in ferrets with insulinoma). Luckily, the incidence of post-surgical diabetes is low, and this should not be consideration for avoiding surgery.

All is not lost, however, for non-surgical candidates with other serious concomitant

disease or animals which are still recovering from a previous surgery. The most common treatment is daily administration of prednisone - a steroid which mimics the actions of cortisol (a hormone normally secreted by the adrenal cortex). Prednisone achieves its effects by causing breakdown of body protein and reformation into glucose by the liver (a process known as *gluconeogenesis*) and by decreasing the utilization of glucose by many body tissues. While an uneasy truce between the actions of insulin and prednisone may be achieved for a while, the prednisone dosage must be continually adjusted upward in order to match the increasing levels of insulin secreted by a growing tumor. Eventually, even high levels of prednisone cannot counteract the effects of the insulin secreted by the tumor, and the ferret is in the unenviable position of facing surgical intervention in a weakened state.

Other drugs have received attention over the years as possible medical adjuncts to prednisone in the antagonism of insulin. The diuretic Proglycem (diazoxide) has been advocated as an adjunct to prednisone as a result of its unique and poorly understood glucogenic effects; however most experienced practitioners today have little use for its minimal effects in the face of significant expense. Chromium (either in the commercially available piccolinate form, or found in minute amounts in Brewer's yeast) has been suggested as a way to stabilize glucose levels. However, controlled studies have not been performed in support of its anecdotal success, and available literature in other species suggests that it may actually result worsen hypoglycemia in some cases.

In a hypoglycemic crisis, such as when an animal is seizing, the instillation of a small amount of a high-sugar compound, such as Karo syrup or honey may elicit a slight rise in blood glucose, occasionally enough to terminate a seizure or ameliorate other signs of severe hypoglycemia. However, this is not a definitive treatment, only a stopgap

measure between your house and your vet's office or emergency clinic.

Insulinoma in short.....

The bottom line for insulinoma is this: if you have middleaged to older ferrets, it is very likely that you will encounter this disease. However, the development of this very treatable condition is certainly not the end of the line for your pet – with early surgical intervention, most ferrets go on to lead relatively normal lives, and many are cured. Medical therapy, although not the best option remains for older ferrets or other non-surgical candidates, and markedly improves the quality of life of later years.

Sidebar: A Pancreatic Primer

Endocrine: Cells that secrete hormones into the bloodstream. In the pancreas, cells of the islets of Langerhans produce a range of hormones (see below) which work on many tissues throughout the body.

Exocrine: Cells that secrete compounds directly outside of themselves (usually into a duct). The acinar cells of the pancreas create and package digestive enzymes which are delivered into the intestine through the pancreatic duct.

Pancreatic islets: Collections of specialized cells scattered in small islands throughout the pancreas. These endocrine cells secrete hormones in response to various metabolic triggers, including glucagon (alpha cells), insulin (beta-cells), somatostatin (gamma cells) and several others.

Acinar cells: Cells within the pancreas which produce and package enzymes used in the intestine to digest protein and starch. If accidentally released into the pancreas as a result of trauma or inflammation, these enzymes will initiate a vicious cycle by digesting the pancreas itself (liberating more

enzymes, etc.) Digestive enzymes aren't really very bright.

Glucose – The metabolizable form of blood sugar which is used as fuel by all of the cells of the body. **Hyperglycemia** is an elevated level of glucose in the blood, **hypoglycemia** is a decreased level of blood glucose.

Insulin – Secreted by the beta cells of the pancreatic islet, insulin is the most important hormone governing glucose regulation. **At the cellular level**, insulin is required for movement of glucose into cells. **In the blood**, insulin decreases the level of glucose as it drives the sugar into the cells. **At the systemic level**, insulin results in conversion of glycogen stores to usable glucose in the liver, as well as mobilization of fat stores for eventual hepatic transformation into glucose.

Glucagon – Secreted by alpha cells of the pancreatic islets, glucagon opposes insulin's actions on blood glucose. In the blood, glucagon raises the blood sugar and at the systemic level, initiates the formation of glycogen from glucose within the liver.