1974

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Canine Insulinoma (A Case Report)

by

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Summary

Canine Insulinoma is a disease of old dogs which results from a functional neoplasm involving the beta cells of the islets of Langerhan's of the pancreas. These are the same cells that are involved in diabetes mellitus where insulin production is decreased instead of increased. The insulinoma dog is usually admitted with signs of weakness, ataxia, restlessness, ravenous appetite, and convulsions. Since the owner is usually concerned about the convulsions, it is easy to be misled into treating the animal for the convulsions, and do nothing more. Blood glucose analysis on all animals presented with convulsions will minimize this mistake. The purpose of this paper is to present a case report and discuss differential diagnoses.

Introduction

All of the signs which are seen with insulinoma are progressive and related to the existing hypoglycemia. The signs can be manifested after fasting, exercise, excitement, after eating, or they may not be related to any of these states. Early in the syndrome this disease is characterized by weakness which usually gets worse with progression of the disease. The first sign is usually posterior weakness which progresses to whole body weakness. The dog may show disorientation, incoordination, and even blindness. Usually the convulsions do not occur until later in the course of the disease. These convulsions tend to become more frequent and more severe as time goes on. The condition is frequently accompanied by increased appetite and consequently a weight gain. Insulinoma has been observed in dogs ranging from six to sixteen years of age. Breed predisposition is still questionable. One study has shown a sex predisposition with 67% occurring in males.

The hypoglycemia seen with insulinoma is a direct result of the hyperinsulinism. Insulin not only affects blood levels of glucose but excess insulin also inhibits gluconeogenesis in the liver. The blood glucose is simply utilized faster than it can be replenished and signs of hypoglycemia are seen. Early in the disease, blood glucose declines slowly and the hypothalamus does not stimulate counter-regulatory hormone release (growth hormone, glucocorticoids, pancreatic glucagon, epinephrine, and norepinephrine) and mild signs of hypoglycemia are seen. This continues and any rapid onset of hypoglycemia early in the course is balanced by the counter-regulatory mechanisms so there are no severe signs associated with this more severe hypoglycemia. However, as this sequence of events continues over weeks, there is an exhaustion of the pituitary-adrenal cortex and medullary counter-regulatory axis. At this time the animal's system can not cope with the severe hypoglycemia and more severe signs are
seen. Things like exercise and fasting can potentiate this sudden drop in blood glucose and the animal’s body is helpless. When this happens, convulsions may be observed.

In the normal animal, it is thought that insulin works in conjunction with a membrane transport system. This facilitated diffusion can increase the glucose intake of most cells (excluding brain) as much as twenty fold. With hyperinsulinism, more glucose is driven into the cells and the blood glucose goes down. The brain’s intake of glucose seems to be more dependent on diffusion through the blood-brain-barrier and is independent of insulin. Therefore, when the blood glucose concentration drops because of increased insulin, it is the brain which suffers and not the other body tissues. The brain, needing glucose to function, becomes less able to extract the oxygen from its blood supply. Therefore, the signs of hypoglycemia which are seen with insulinoma are almost identical to anoxia. The dog can thus become comatose following a convulsion and can suffer irreversible (anoxic) brain damage.

Case Report

On Oct. 2, 1973, a 16-year-old spayed female Labrador-English Pointer cross was presented to Strange Memorial Clinic with a history of convulsions. The referring veterinarian had first seen the dog on Sept. 4, 1973 at which time the owner described a peculiar weakness and fainting in the morning after the dog had been outside. This had been going on for several weeks prior to presentation. The dog had a heart murmur. It was thought that these spells were related to the murmur and digitalis was prescribed. Two weeks later the dog was returned. At this time it was admitted and had a convulsion the next morning. The seizures were characterized by shaking and severe twitching of the head, falling over backwards and then repeating this several times. At this time a fasting blood sample was taken and hypoglycemia was evident with a blood glucose of 16 mg%. It was suggested at this time that the dog be fed late at night and early in the morning and that sugar water be given. This helped reduce the severity of the convulsions, but not significantly. A tentative diagnosis of canine insulinoma was made and the dog was referred then to the Iowa State University College of Veterinary Medicine for confirmation.

Upon entrance to the clinic a routine physical examination was done. Multiple small skin growths were observed on the legs and around the eyes. There was a small abscess on the dorsum of the back and the teeth had heavy tartar accumulation. No heart murmur was detected at this time. A fasting blood sample was taken and the resulting blood glucose concentration was 27 mg%. The next morning a glucose tolerance test was run which was suggestive of insulinoma. The results were as follows:

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<tr>
<th>Time (minutes)</th>
<th>Blood Glucose (mg. %)</th>
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<tr>
<td>0</td>
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<td>30</td>
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The dog went home at this time and on October 30, the owners returned the dog to the clinic for euthanasia. The dog was still in good flesh but the convulsions were regular and becoming more severe. At necropsy, there was a neoplastic mass in the pancreas. Histopathology revealed that the mass was surrounded by fibrous connective tissue but there was obvious invasion into surrounding acinar tissue. The neoplastic cells were divided into numerous lobules by fibrous connective tissue. The tumor cells were growing in sheets in some areas and were individually discrete in other areas. They had a moderate amount of cytoplasm. Mitotic figures were common but not numerous. The diagnosis was an islet cell carcinoma and the above

* Histopathology was done by Dr. Flatt, Associate Professor of Veterinary Pathology at Iowa State University.

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histopathologic findings are typical for this disease.

**Discussion**

The first and most important step in differentiating insulinoma from other diseases is the blood glucose value. A normal fasting blood glucose is 70 to 110 mg% (Orthotoluidine method) in the dog. Once it is established that hypoglycemia is present, and that the convulsions are a result of low blood sugar, causes of hypoglycemia must be considered. Causes of hypoglycemia fit into two classes: functional and organic.

Convulsions caused by functional hypoglycemia are usually seen in hunting dogs or toy breeds as a result of a temporary decrease in blood sugar. Chronic starvation, malabsorption, severe liver damage, poisons, or deficient glycogen storage can lead to this condition. These animals are usually on a high carbohydrate diet. Any hard work or stress can cause the hypoglycemic state and the liver is unable to mobilize stored glycogen. A convulsion can and often does result. Most causes of hypoglycemia are functional. Functional hypoglycemia can be differentiated from organic causes with a **tolbutamide tolerance test**. This can be dangerous in the dog because tolbutamide causes a massive outpouring of insulin which lasts for about 18 hours and profound hypoglycemia will often cause convulsions and shock. Another way to differentiate these which is more practical but less reliable is stressing or working the dog and measuring pre-stress and post-stress glucose values. A drop in blood glucose is an indication of a functional hypoglycemia. These animals can have fasting blood glucose values in the normal range before working or stressing.

Organic causes of hypoglycemia include overtreating diabetes mellitus, severe liver disease, kidney problems, hypoadrenalcorticism, hypopituitarism, and insulinoma. An oral glucose tolerance test is very helpful in most cases. The dog is fasted for 12 to 24 hours and then given dextrose orally at the rate of 1.0 gram per pound of body weight. Blood samples are taken pre-administration and at 15, 30, 60, 120, 180 minute intervals. A simple graph of results that are obtained with a normal dog, diabetes mellitus, and canine insulinoma follows:

When glucose is given orally to a normal dog, the blood glucose concentration rises above 100 mg% and returns to normal within two hours. In diabetes mellitus, the blood glucose rises and may be elevated for several hours. Dogs with insulinoma however, seldom show a rise in blood glucose over 100 mg% and the concentration usually drops below pre-administration levels within two hours.

Other diagnoses that may be made early in the syndrome are lumbar intervertebral disc herniation, cervical disc herniation, idiopathic epilepsy, canine distemper, and brain tumors. These cases, recognition of the role of hypoglycemia was long delayed and unsuccessful trials of anticonvulsants were usually the result.

Other tests can be performed and these include I.V. glucose tolerance test, which is more reliable than oral tests, I.V. glucagon tolerance test, leucine tolerance test, and measurement of insulin in the blood. This is done by quantitating the amount of hormone in the plasma by radioimmunoassay. Increased insulin is an indication of a functional beta cell carcinoma. Normal fasting plasma levels of immunoreactive insulin are 0-54uU/ml and in the dog with insulinoma the values range from 11-337uU/ml. This value can be compared with the fasting blood glucose value to get an insulin/glucose ratio. Control dogs may have an I/G ratio of 0-52 with insulinoma dogs having a ratio of 41-1006. This has been of value in

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diagnosing functional insulinomas. One study has indicated 90% of the carcinomas and 60% of the adenomas are functional. This study also showed that 56% were carcinomas and 44% were adenomas in the dog. Metastasis was usually to the liver and surrounding lymph nodes. These metastatic sites were found to be functional by the responsiveness to tolbutamid following excision of the primary neoplasm. Treatment of insulinoma is difficult. Early in the disease surgery can be performed but by the time a diagnosis is made, most of these will have metastasized. Dextrose as a 50% solution will usually help bring a dog out of a convulsive state but this is only temporary. Drugs with hyperglycemic properties and drugs with antitumor properties are being tried but most have harmful side affects and are under further investigation. Glucocorticoids and frequent feedings have been partially successful. Epinephrine at the rate of 0.5 to 1.0 ml sub-cutaneously, which releases glucose from the liver has also helped. The administration of alloxan, which causes selective necrosis of the beta cells in the normal pancreas, has been unsuccessful in the dog as a therapeutic measure. Cause of death is usually glucose-unresponsive seizures and coma. Brain damage can also occur without death in these severe states of hypoglycemia. Tentative diagnosis of insulinoma, which is considered rare, is made on the basis of history, plus the finding of a rapid response to intravenous glucose administration if seen during a crisis and finding blood glucose values less than 50 mg%.

Bibliography

Junior Students Tour Drug Companies

Forty-nine ISU junior veterinary students, two wives, two husbands, and Drs. R. M. Hogle and R. W. Carithers left Sunday, Feb. 24 by bus for a week's tour of the Eli Lilly, Parke-Davis, and Upjohn Pharmaceutical Companies. This is an annual trip taken by junior veterinary students during the spring quarterbreak. The group arrived in Indianapolis, Indiana Sunday evening. Monday was spent at Elanco's (a division of Eli Lilly) Greenfield Research Center where we were given tours of the research facilities. Tuesday morning we visited the Lily Information Center where we were shown a movie of the company's formation. Tuesday afternoon we journeyed to Detroit, Michigan. Both the research facilities in Ann Arbor and the production plant in Detroit, of Parke-Davis were toured on Wednesday. Thursday morning we again traveled by bus to Kalamazoo, Michigan for tours on Friday of the Upjohn research and manufacturing facilities. All three companies allowed for seminar-discussion sessions in which research, manufacturing, and marketing representatives of the companies expressed the philosophies of their respective companies and answered our many questions regarding the structure and function of a drug company, legalities and procedures in the approval and marketing of drugs, and the veterinarian's role in the company. These sessions and tours were very informative and interesting.

We all felt that the tours were quite educational and a very enjoyable experience. We would like to thank Eli Lilly, Parke-Davis, and Upjohn for sponsoring these trips and hope that they continue to provide this opportunity for the succeeding junior classes. We would also like to thank those Iowa veterinary practitioners who contributed to the Veterinary College Travel Fund and thus aided in making this trip possible.

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