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The Use of Serum Trypsin-like Immunoreactivity for the Diagnosis of Canine Exocrine Pancreatic Insufficiency

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Introduction

Exocrine pancreatic insufficiency (EPI) is an important cause of malassimilation in the dog. Due to the unreliability of available diagnostic procedures in the past the prevalence of EPI has probably been exaggerated. A new procedure has recently been developed and is proving to be highly sensitive and highly specific for the measurement of exocrine pancreatic function. This test, a radioimmunoassay of serum trypsin-like immunoreactivity, shows promise for more accurately distinguishing between EPI and small intestinal disease as the cause of malassimilation.

Exocrine Pancreatic Insufficiency

A failure of the pancreas to produce and secrete adequate digestive enzymes results in nutrient maldigestion and subsequent malnutrition. This syndrome is known as exocrine pancreatic insufficiency. Juvenile pancreatic acinar atrophy, chronic relapsing pancreatitis, and, rarely, severe acute pancreatitis and neoplasia can lead to this condition. The pancreas has considerable functional reserve but when greater than 90% of the acinar mass is destroyed or nonfunctional the concentrations of alpha-amylase, pancreatic proteases, and lipase secreted into the small intestine fall below critical levels. Maldigestion of starches, proteins and triglycerides ensues and clinical signs of malassimilation and malnutrition appear. Clinical signs of EPI include diarrhea, steatorrhea, weight loss, ravenous appetite, voluminous and malodorous fecal mass often containing undigested food elements, excessive borborygms, coprophagia, abdominal distension and general signs of malnutrition. Affected dogs usually remain active and alert. It is difficult to distinguish on the basis of these clinical signs whether the malassimilation is of pancreatic or small intestinal origin. Since treatment for exocrine pancreatic insufficiency consists of expensive oral pancreatic enzyme supplementation, it is important to distinguish those dogs that will benefit from this therapy from those which will not.

Previously Available Diagnostic Tests

A variety of tests have been utilized to aid in the diagnosis of EPI which include the microscopic examination of feces, measurement of fecal proteolytic activity and oral fat absorption tests with and without added digestive enzymes. More recently a synthetic peptide (BT-PABA) has been utilized to evaluate pancreatic output of chymotrypsin. The sensitivity and specificity of each of these methods as well as their practicality have been questioned and a search for a more satisfactory test continues.

Radioimmunoassay of Trypsin-like Immunoreactivity

Recent studies and case reports of a radioimmunoassay of trypsin-like immunoreactivity (TLI) in canine serum suggest that it is a more sensitive and specific indicator of exocrine pancreatic insufficiency. The classical radioimmunoassay techniques employed make use of antibodies raised in rabbits against canine cationic trypsin. The immunoreactivity of the canine patient serum refers to the concentration of proteins recognized by these antibodies. Trypsinogen, free trypsin, and trypsin complexed with inhibitor molecules bind these antibodies equally well, hence the term “trypsin-like immunoreactiv-
ity. In the absence of pancreatitis, however, only trypsinogen is present in serum. There is no significant cross-reactivity with anionic trypsinogen and trypsin, nor chymotrypsin. As trypsinogen is produced and secreted only by pancreatic acinar cells this assay is pancreas specific.

Trypsinogen, the inactive zymogen of trypsin, is produced by pancreatic acinar cells and secreted into the small intestine. Enterokinase in the small intestine cleaves the trypsinogen into the active enzyme. No detectable levels of trypsinogen nor trypsin are absorbed from the intestinal lumen. Rather, 0.1% to 0.01% of the trypsinogen synthesized daily leaks from the pancreas directly into the bloodstream. Present as cationic and anionic isoenzymes, the trypsinogen has a very short half-life. It is rapidly filtered at the glomerulus, especially the cationic form, and is metabolized by renal tubular cells. This leakage from the pancreas results in a consistent low level of trypsinogen being present in the serum of normal dogs. A single serum sample is all that is needed from the patient. This sample should be drawn after a fast of at least twelve hours. TLI is stable in serum for several days at room temperature so it can be shipped to a laboratory with no special packing considerations. Prolonged exposure to heat during shipping has been blamed for some equivocal results seen in one laboratory. Dogs already on pancreatic enzyme supplementation do not need to undergo a withdrawal period as this therapy has no effect on the assay.

All of the studies of TLI have revealed it to be highly sensitive and highly specific for exocrine pancreatic insufficiency. Compared to normal dogs and dogs exhibiting steatorrhea secondary to small intestinal disease, the TLI levels in dogs with EPI are consistently and significantly subnormal. Dogs with clinical EPI have had TLI concentrations <2.5 ug/L. Values in normal dogs and those with small intestinal disease are not significantly different and have been in the range of 5.0 ug/L to 35.0 ug/L.

Occasionally, results fall into a "gray zone" between 2.5 ug/L and 5.0 ug/L. The situations in which this may occur have been reasonably explained. In some dogs with EPI a transient increase in serum TLI is seen after feeding. These values usually return to <2.5 ug/L within three hours. This phenomenon stresses the importance of sampling only after fasting the animal. Dogs which have experienced chronic relapsing pancreatitis may have values in the 2.5 to 3.0 ug/L range with some showing clinical signs of EPI and others not, depending on extra-pancreatic digestive capabilities. Higher levels seen with chronic relapsing pancreatitis may be attributable to inflammation of residual pancreatic tissue. Some dogs with subclinical EPI have measured TLI >3.0 ug/L. Dogs tested earlier in the course of the disease than those used in the reported studies may show higher concentrations even when the EPI is clinical. It is also possible for a normal dog to have low TLI if it has been on a prolonged low protein diet. The values in these dogs probably will not fall below 4.0 ug/L.

The assay of serum TLI does have its limitations in certain situations. A case of EPI secondary to pancreatic duct obstruction can still have normal serum TLI as synthesis of trypsinogen is not the underlying problem. The same is true in animals with a congenital deficiency of other pancreatic enzymes or intestinal enterokinases, although these conditions have not yet been reported in dogs.

Increased serum trypsin-like immunoreactivity can be seen in early stages of acute pancreatitis, with severe renal dysfunction, and possibly in cases of extreme malnutrition. The use of this parameter to diagnose pancreatitis has been considered but has disadvantages for use in azotemic patients just as amylase and lipase determinations do.

Conclusions

There is an increasing number of reports supporting the usefulness of trypsin-like immunoreactivity in diagnosing exocrine pancreatic insufficiency in the canine patient. In any case of steatorrhea it can be used to determine if small intestinal disease or pancreatic insufficiency is the underlying cause of the malassimilation. Currently available in only a small number of laboratories in the United States, it has not gained widespread recognition and acceptance. The assay's high specificity, sensitivity, and ease should soon make it highly popular in confirming suspected cases of exocrine pancreatic insufficiency.
References


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