EXOCRINE PANCREATIC INSUFFICIENCY - COMMONLY UNDIAGNOSED!

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Exocrine pancreatic insufficiency (EPI) is an alimentary tract disorder characterized by inadequate production of digestive enzymes from pancreatic acinar cells, leading to characteristic clinical signs of weight loss, with or without polyphagia, diarrhea, steatorrhea, and poor-quality hair coat. In rare cases, EPI can be caused by an obstruction of the pancreatic duct secondary to pancreatic adenocarcinoma. Insufficient synthesis of pancreatic digestive enzymes can be due to destruction of acinar cells resulting from chronic pancreatitis (approximately 50% of cases in dogs and most cases in cats) or can be due to idiopathic pancreatic acinar atrophy (PAA; most common cause of exocrine pancreatic insufficiency in German Shepherd dogs).

EPIDEMIOLOGY AND GENETICS

Several canine breeds have been identified at risk for development of EPI, including German Shepherd dogs, rough-coated Collies, Cavalier King Charles Spaniels, Chows, Cocker Spaniels, Cairn terriers, and West Highland white terriers. The association of German Shepherd dogs and EPI is well recognized and was initially proposed to be an autosomal recessive trait; however, test mating of 2 symptomatic German Shepherds failed to support this hypothesis. Genome-wide association studies in German Shepherds revealed several single nucleotide polymorphisms associated with pancreatic acinar atrophy, many of which were located on chromosome 12. Additional studies are warranted in this area.

PATHOGENESIS

The most common cause of EPI in dogs is pancreatic acinar atrophy; however, chronic pancreatitis is a more common cause in cats. Other causes of EPI in both species include pancreatic duct obstruction and pancreatic neoplasia. Pancreatic acinar atrophy (PAA) is characterized by selective destruction of pancreatic acinar cells and their replacement with adipose and connective tissue in the absence of marked inflammation or fibrosis. An immune-mediated cause is proposed to be the most common cause of pancreatic acinar atrophy and is associated with a lymphocytic infiltration of the pancreas with circulating autoantibodies against pancreatic acinar cells. Recent evidence has questioned the role of chronic pancreatitis as the most common cause of EPI in cats and there is evidence that pancreatic acinar atrophy is also an important cause of EPI in cats, like that in dogs. *Eurytrema procyonis* (racoon pancreatic fluke) has also been described as a potential cause of EPI in cats.

The onset of clinical signs is typically recognized in young adult animals (median age 3 years), although any age of dog can be affected. Clinical signs are caused by defective digestion and absorption of dietary macronutrients (protein, fat, starch). Clinical signs of EPI only emerge once > 90% of pancreatic acinar cell mass is lost. The undigested nutrients within the lumen of the intestine become substrates for bacterial fermentation predisposing to intestinal dysbiosis, further exacerbating diarrhea, flatulence, and abdominal discomfort. Cobalamin deficiency is also associated with intestinal dysbiosis and lack of intrinsic factor, the latter phenomenon more likely in cats.

DIAGNOSIS

Dogs with pancreatic acinar atrophy may be asymptomatic (subclinical) at the time of diagnosis or may have more overt signs including weight loss despite polyphagia, increased fecal volume, steatorrhea, and flatulence. Other features include pica, poor coat quality, changes in behavior, and abdominal discomfort. Cats with EPI show fewer "classic" features of EPI compared to dogs and weight loss is the most documented clinical sign. Other less frequent clinical signs include vomiting, anorexia, and polyuria/polydipsia secondary to diabetes mellitus. Affected animals are in typical thin body condition with decreased muscle mass, poor hair-coat quality, and greasy "soiling" of the hair coat, particularly in cats.

LABORATORY TESTING

There are no specific abnormalities in the CBC or chemistry panel that are indicative of EPI, unless the patient is diabetic. Abdominal ultrasound may reveal reduced pancreatic thickness associated with atrophy; however, this is an insensitive feature of EPI and the disorder should never be ruled out based on a normal pancreatic ultrasonographic appearance. Ultrasonographic findings of concurrent intestinal wall changes is common, particularly in cats.

Trypsin-like immunoreactivity

Fecal screening (centrifugation flotation, fecal PCR, or fecal antigen testing) is warranted to rule out intestinal parasites; however, testing of exocrine pancreatic function is warranted. The diagnostic test of choice is the trypsin-like immunoreactivity (TLI) test which measures trypsinogen and trypsin concentrations in the blood. The test is species specific and is highly sensitive. Serum TLI is detected in the serum of all normal dogs and cats with a functional exocrine pancreatic mass; however, serum TLI concentrations are dramatically reduced with EPI. In dogs a cTLI ≤ 5.5 μg/L and in cats a fTLI < 8.0 μg/L is considered diagnostic for EPI. Testing for EPI should ideally be done in the fasted patient; however, the increase after feeding in both dogs and cats rarely affects clinical interpretation of the result. Increased TLI concentrations can be seen in association with pancreatitis, complicating the diagnosis in affected dogs. In addition, markedly reduced glomerular filtration rate can increase TLI concentrations; however, the test is not affected in dogs and cats with mild to moderate renal disease.

Other assays for diagnosing EPI

Assays of fecal proteolytic activity using casein-based substrates have been used to diagnose EPI in both dogs and cats; however, fecal proteolytic activity is associated with false-positive and false-negative test results and should only be used in exotic species for which a serum TLI test is not available. An assay for the measurement of fecal elastase has recently been validated for the dog. However, this test is associated with a high rate of false-positive test results and cannot be recommended at this point. Microscopic examination of feces for undigested food, assessment of fecal proteolytic activity and the plasma turbidity test are unreliable and *not* recommended.

Serum cobalamin and folate

Measurement of cobalamin and folate concentrations is pivotal in all dogs and cats with EPI. Cobalamin (vitamin B12) is frequently deficient in both dogs and cats with EPI and can lead to

treatment failure if not addressed. Alterations of B12 and folate concentrations can also be reflective of intestinal dysbiosis in dogs or lack of intrinsic factor in cats.

TREATMENT

Pancreatic Enzyme Replacement Therapy

Supplementation of the diet with pancreatic enzyme replacement of animal origin is the mainstay of therapy. Both enteric-coated and non-enteric coated formulations are available, and the author prefers to begin therapy with non-enteric coated formulations to reduce cost.

Powdered or capsule formulations can be administered. One can mix enzyme powder in food at a dosage of 1 teaspoon/10 kg body weight with each meal while feeding 2 meals daily to promote weight gain. Preincubation of enzymes with food does *not* improve the effectiveness of oral enzyme therapy. A well-documented adverse effect of pancreatic enzyme replacement therapy is oral bleeding, and one should avoid sprinkling pancreatic enzyme powder on top of the animal's kibble to reduce the risk of this complication. In pets fed a kibble diet, one can mix the enzyme powder in a tablespoon of canned food which is added to the kibble at the time of feeding. Capsule formulations will also reduce the risk of oral bleeding associated with digestion of the oral mucosa. The cost of pancreatic enzyme replacement can be high, and owners can frequently reduce the dose of enzyme replacement therapy in small increments every 2 weeks following restoration of body weight and resolution of diarrhea. Close monitoring of body weight and stool quality will allow the owner to reduce the enzyme replacement therapy to the lowest effective dose which is often markedly lower than that initiated. Administration of replacement enzyme powder can be more challenging in cats, and it is often easier to supplement the enzymes in capsule form. Most cats are fed free choice, and it is impossible to co-administer enzyme replacement therapy with all meals. Careful consideration of transitioning the cat to meal feeding is a viable consideration in affected cats. Fresh raw beef or pork pancreas is a viable consideration for owners who can gain easy access to the raw pancreas at a butcher or abattoir; however, the risks of bacterial and parasitic contamination must be discussed with the owner. Raw pancreas can be kept frozen for months without losing enzymatic activity.

Dietary Therapy

Fat-restricted and high-fiber diets should be avoided, and most affected animals can be maintained on a highly digestible "intestinal" formula. Modification of the diet to a hydrolysate or elimination diet containing a novel single protein source can be considered for dogs and cats that fail to respond to the intestinal formula. A beneficial response to an elimination diet might reflect an underlying chronic enteropathy.

Cobalamin supplementation

> 60% of dogs and virtually all cats with EPI are cobalamin deficient and require cobalamin supplementation (both oral and parenteral cobalamin supplementations are effective). The most common cause for the cobalamin deficiency is due to increased update by enteric bacteria and due to reduced concentrations of intrinsic factor. The author routinely supplements cobalamin when concentrations in serum are < 400 ng/L.

Micronutrient supplementation

Severely malnourished dogs may also require supplementation with tocopherol. Body stores of other fat-soluble vitamins are probably also decreased in dogs and cats with EPI, but supplementation does not appear to be crucial. A case report of an EPI cat with vitamin K deficiency has also been published.

CONSIDERATIONS FOR LACK OF RESPONSE TO PANCREATIC ENZYME SUPPLEMENTATION

The most common considerations for lack of response to enzyme replacement therapy include client compliance (not giving the enzyme supplementation with all meals), poor quality pancreatic enzyme product (avoid use of plant-based products), hypocobalaminemia, digestion of non-enteric coated formulations in the acid milieu of the stomach (co-administration with acid suppressants such as omeprazole or administration of an enteric coated formulation can prevent this), or a concurrent disorder such as chronic enteropathy warranting a different diet and/or immunosuppressive therapy.

SURGICAL CONSIDERATIONS

Mesenteric torsion has been reported in German shepherd dogs with EPI in Finland but not North America.

PROGNOSIS

Diarrhea improves markedly in most affected animals with fecal consistency typically normalizing within 1-2 weeks. Body weight is also typically regained in an expedient fashion. Patients that fail to respond after 2 weeks of enzyme therapy and cobalamin supplementation (if indicated) should be evaluated for the abovementioned considerations that can cause a suboptimal response to therapy. Owners should avoid administering > 2 teaspoons of enzyme replacement powder per cup of food.

The long-term prognosis for dogs with EPI is generally favourable with 60% demonstrating a complete response to therapy, 17% demonstrating a partial response, and 23% demonstrating a poor response. Lifelong supplementation of enzyme powder or capsules is required in most affected animals; however, the amount of replacement therapy can be gradually decreased over time to a lower “maintenance” dose that prevents weight loss and maintains a normal stool consistency.

SUGGESTED READING

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