Case Report
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Suspected Isolated Pancreatic Enzyme Deficiencies in Dogs

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Key words: Chronic diarrhea; Exocrine pancratic insufficiency; Gastroenterology; Isolated pancreatic lipase deficiency; Pancreas.

Case 1

A 6-month-old, male intact, German Shepherd Dog (GSD) was examined for a 3 month history of chronically loose feces since the owner acquired him at 12 weeks of age. Over the 3 month period the dog maintained an excellent appetite with little weight gain and had persistently abnormal feces. The consistency of feces ranged from soft to liquid diarrhea. The dog tested positive for *Giardia* spp. on multiple occasions despite multiple treatments with fenbendazole and metronidazole. Additional therapies including tylosin and probiotics resulted in transient or no improvement. Two weeks before examination, the dog started vomiting once every 5 days.

On examination, the dog weighed 22 kg with a body condition score of 3/9. Physical abnormalities included brachygnathism with malocclusion lesions on the lower lip and hard palate, erythema with occasional pustules on its ventrum, consistent with a superficial pyoderma, and pain when extending both hips suggestive of bilateral hip dysplasia. Abdominal palpation was nonpainful and rectal examination revealed only soft feces of normal color. Complete blood count (CBC), serum chemistry, and electrolytes were within the reference interval with the exception of a mild increase in serum phosphorus (7.6 mg/dL; reference interval, 2.1–6.3 mg/dL), which was consistent with the dog's age. Abdominal ultrasound examination did not reveal abnormalities. The spleen was mottled and multiple lymph nodes were visible, but of normal echogenicity and consistent with dog's age. Serum concentrations of bile acids before and after eating were 1.6 μmol/L (reference interval 0–28 μmol/L) and <1.0 μmol/L (reference interval 0–28 μmol/L), and cortisol (2.3 μg/dL, reference interval 1–5 μg/dL), cobalamin (513 ng/L; reference interval 251–908 ng/L), and folate (20.7 μg/L, reference interval 7.7–24.4 μg/L) were all within the reference interval. The dog's serum pancreatic lipase immunoreactivity (cPLI)[a] was less than the lower limit of detection (<30 μg/L, reference interval 30–200 μg/L) and trypsin-like immunoreactivity (TLI) was below the reference interval (5.2 μg/L, reference interval 5.7–45.2 μg/L), a level not associated with clinical signs of exocrine pancreatic insufficiency (EPI).[1–3] The dog was initially discharged with instructions to administer pyrantel pamoate. One week later, the dog's vomiting had improved but it continued to have soft feces. The dog was treated with pancreatic enzyme supplementation[b] (PES) (1–1.5 teaspoons with each meal). One month after starting the administration of PES the owner reported the dog to be passing normal feces for the first time in its life with steady weight gain. With continual PES, 3 months later the dog was reported to have normal feces with no episodes of diarrhea. One year and 8 months after the initiation of PES, the dog was reported to be clinically normal with no more soft feces or diarrhea and its serum TLI concentration was unchanged at 5.6 μg/L (reference interval 5.7–45.2 μg/L).

Case 2

A 5-month-old, male intact, Rough-Coated Collie (RCC) was examined for a 2 month history of waxing and waning watery diarrhea since owner acquired him at 8 weeks of age. Within days of acquiring the puppy, it was dewormed with pyrantel pamoate. Two weeks later, it was treated with sulfadimethoxine after testing positive for *Coccidia* spp. Over the 2 month period, the dog's diarrhea would only temporarily resolve after deworming (fenbendazole), administration of antibiotics (sulfadimethoxine, metronidazole, ampicillin, and tylosin), multiple diet trials, and feeding of probiotics. The dog tested fecal negative for *Clostridium perfringens* enterotoxin (enzyme-linked immunosorbent assay or ELISA[c]) and *Giardia* spp. (ELISA[c] and immunofluorescence assay or IFA[c]). The dog's appetite was described as excellent, but weight gain was marginal.

On examination, the dog weighed 9.6 kg with a body condition score of 4/9 and an overall poor haircoat. The remainder of its physical examination, including rectal examination, did not reveal abnormalities. CBC, serum chemistry, and electrolytes were within the reference interval with the exception of a mild increase in serum phosphorus (8.2 mg/dL; reference interval, 2.1–6.3 mg/dL) consistent with a growing puppy. Abdominal ultrasound examination indicated an empty small intestine with a moderate amount of gas. The puppy was dewormed with fenbendazole pending the results of its gastrointestinal panel to rule out malabsorption or EPI. The dog's serum cobalamin (830 ng/L; reference interval 251–908 ng/L), folate (16.9 μg/L, reference interval 7.7–24.4 μg/L), and

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TLI (6.5 μg/L, reference interval 5.7–45.2 μg/L) were all within the reference interval. One week after fenbendazole the dog's feces normalized. However, 3 days later the owner reported the dog's watery diarrhea returned, and based on the dog's PLI[a] below the limit of detection (<30 μg/L, reference interval 30–200 μg/L) a trial on PES[b] (0.75 teaspoons with each meal) was initiated for a suspected isolated pancreatic enzyme deficiency.[4] Three weeks after supplementing the dog's meal with pancreatic enzymes, the owner reported that the dog's diarrhea had promptly resolved and its haircoat was normal for the first time. Supplementation with pancreatic enzyme continued and 4 months later the dog's feces remained consistently normal. The dog's TLI remained within the reference interval (7.8 μg/L, reference interval 5.7–45.2 μg/L). One and a half years after the initiation of PES, the dog remains clinically normal with complete resolution of the dog's soft feces/diarrhea and an improved haircoat. The dog's serum TLI concentration was unchanged at 10.6 μg/L (reference interval 5.7–45.2 μg/L). The only reported relapse of the dog's diarrhea occurred immediately after the owners discontinued the PES. The dog's diarrhea subsequently resolved with re-introduction of PES.

Case 3

A 1.5-year-old, male intact, GSD was examined for a chronic (lifelong) history of soft feces or diarrhea. One month before examination, the dog's diarrhea was persistently watery and he had lost approximately 2 kg. The dog has a history of atopic dermatitis, superficial pyoderma, repeated episodes of otitis externa, and dietary indiscretion. The owners described the dog as having diarrhea since they acquired the dog as a puppy. The dog's energy level and appetite have always been excellent. The dog tested positive for *Giardia* spp. at 3 months of age and was treated with fenbendazole. After treatment with fenbendazole the dog's diarrhea continued. Previous empirical therapies have included rice, yogurt, and Metamucil®.[d]

The dog weighed 44 kg with a body condition score of 4–5/9. Physical examination abnormalities included erythematous ears with a mild amount of waxy discharge, fecal staining around its anus, and splenomegaly upon abdominal palpation. CBC, serum chemistry, and electrolytes were within the reference range with the exception of a mild neutrophilia (11,573/μL; reference interval 2,600–10,000). Abdominal ultrasound examination revealed a subjectively enlarged spleen of normal echogenicity. The splenomegaly was attributed to sedation with acepromazine. At discharge, the dog was prescribed PES[b] (2 teaspoons with each meal) for presumptive EPI pending the cobalamin, folate, and TLI results and a diet trial with Royal Canin Fish and Potato. Two days after the start of PES and diet trial, the owner reported the dog to be passing normal feces for the first time in its life. The dog's serum concentrations of cobalamin (354 ng/L; reference interval 251–908 ng/L), folate (10.2 μg/L, reference interval 7.7–24.4 μg/L, and TLI (9.9 μg/L, reference interval 5.7–45.2 μg/L) were all within the reference interval. Based on the normal TLI, the PES was discontinued while continuing the novel protein diet. Within 3 days of discontinuation of PES, the dog developed liquid diarrhea. The owner again fed the PES and the dogs feces immediately returned to normal. Retrospectively, the dog's serum PLI was evaluated through the referring veterinarian after the dog's clinical response to PES to rule out a suspected isolated pancreatic enzyme deficiency. The dog's cPLI[a] was low normal at 46 μg/L, (reference interval 30–200 μg/L). One year after initial evaluation and the initiation of PES the dog was reported to have gained weight and remained clinically normal with resolution of any soft feces or diarrhea. Its serum TLI concentration remains unchanged at 9.5 μg/L (reference interval 5.7–45.2 μg/L).

Discussion

The clinical signs of polyphagia, weight loss, and soft voluminous feces in young adult dogs (median, 3 years) of predisposed breeds such as GSDs and RCCs often result in the diagnosis of EPI.[5–7] EPI is commonly associated with pancreatic acinar atrophy that is likely inherited.[8] The diagnosis of EPI is established based on consistent clinical signs, characteristically low (<2.5 μg/L; median 0.7 μg/L; range 0.5–1.5 μg/L) serum TLI[1–3] and resolution of clinical signs following supplementation with pancreatic enzymes. Subclinical EPI (SEPI) is also recognized in dogs and is characterized by the absence of clinical signs but, a repeatedly low serum TLI (<5 μg/L) with partial acinar pancreatic atrophy confirmed by pancreatic biopsy.[9,10] Both EPI and SEPI are thought to have an autoimmune etiology with the gradual destruction of acinar cells by the infiltration of lymphocytes. The progression of SEPI to EPI is variable. Similar breeds of dogs are overrepresented in both conditions.[11]

Isolated pancreatic lipase deficiencies (IPLD) are rare in dogs based on the paucity of reported cases. There is a single case report describing a 4-month-old puppy with a suspected isolated pancreatic enzyme deficiency.[4] The puppy had clinical signs suggestive of EPI but normal serum TLI concentration (7.1 μg/L). Based on a low serum cPLI (<29 μg/L) and dramatic clinical response to PES, this puppy was diagnosed with a suspected IPLD.

Isolated enzyme deficiencies of the pancreas in humans are rare in children and include isolated deficiencies of pancreatic lipase,[12,13] colipase,[14] or combined lipase-colipase,[15,16] trypsinogen,[17] or amylase.[18] In these children isolated deficiencies of specific acinar cell enzymes were described as persistent, nonprogressive, and clinical signs (steatorrhea) resolved with PES.

Published reports of children diagnosed with an IPLD are limited to case reports, including reports in siblings, supporting a suspected congenital origin.[13,19–21] In humans, pancreatic function is assessed directly through pancreatic stimulation with pancreozymin-secretin. A documented low or absent lipase activity in the duodenum is consistent with an IPLD.[12,22]

Over a 1 year period, November 2010 to October 2011, three unrelated young dogs were examined for chronic diarrhea. After a complete work-up, all puppies were diagnosed with a suspected isolated pancreatic enzyme deficiency. The clinical history, physical exam findings, and diagnostic testing were remarkably constant in all 3 dogs, as well as consistent with the initial case report in a 4-month-old puppy.[4] All dogs were reported to have a lifelong history of diarrhea, which was initially noted by the owners and evaluated by a veterinarian between 8–12 weeks of age. All 3 dogs had a history of chronic intestinal parasitism nonresponsive to appropriate treatment and an excellent appetite with marginal weight gain. Their serum TLI concentrations ranged from 5.2 to 9.9 μg/L making EPI an unlikely cause of diarrhea. Dogs with clinical signs of EPI have a median serum TLI concentration of 0.7 μg/L (range 0.5–1.5 μg/L) versus 10.7 μg/L (range 5–46 μg/L) in healthy dogs.[2] All three dogs had a low-normal serum cPLI[a] concentrations (<30–46 μg/L) and diarrhea responsive to PES.

In the group of dogs reported in this case series, follow-up ranged from 12 to 20 months. None of the dogs had progressive clinical signs or a decline in exocrine pancreatic function based on their unchanged serum TLI concentrations. However, further follow-up beyond eight years would be necessary to rule out the development EPI later in life.[2,10] The main goal of our long-term follow-up was to determine whether these dogs' serum TLI concentrations would further decline to values supportive of EPI. Therefore, only serum TLI and not Spec cPL™ assays were reevaluated in each dog.

Assessment of exocrine pancreatic function in dogs is limited to indirect measurements of serum concentrations of pancreatic-specific trypsin and trypsinogen or lipase. Canine TLI concentrations are highly sensitive and specific for the diagnosis of EPI in dogs.[3] Serum cPLI concentrations are widely distributive in dogs. Dogs diagnosed with EPI have serum cPLI concentrations ranging from 0.1 to 1.4 μg/L (median 0.1 μg/L) versus healthy dogs ranging from 1.4 to 270.6 μg/L (median 16.3 μg/L).[2] Despite the cPLI assay being specific for pancreatic lipase,[23,24] many healthy dogs have cPLI concentrations below the detection limit of the Spec cPL™ (30 μg/L). For this reason, serum cPLI concentrations are not used to diagnose EPI in dogs.[2] However, in these 3 dogs with chronic clinical signs of maldigestive diarrhea, normal serum TLI concentrations, low-normal serum Spec cPL™, and dramatic response to PES suggests an isolated either partial or complete pancreatic enzyme deficiency. The exocrine pancreas has a large reserve capacity and it is not until 90% of its secretory capacity is lost that clinical signs of maldigestion occur.[25] Therefore, in dogs with clinical signs of maldigestion a significant loss in exocrine pancreatic function is likely. All 3 dogs developed clinical signs at a much younger age than most dogs with EPI, further supporting that an isolated pancreatic enzyme deficiency in dogs is a congenital condition distinct from EPI.[4]

In summary, this case series of young dogs supports that, as in humans, the diagnosis of a suspected isolated pancreatic enzyme deficiency in dogs is uncommon and maybe a nonprogressive, congenital condition distinct from EPI. However, based on the signalment of these 3 dogs it may be over-represented in dog breeds predisposed to EPI. Further studies are necessary to more completely understand isolated pancreatic enzyme deficiencies in dogs, including its overall prevalence and prevalence in breeds in which EPI is overrepresented, the pathophysiology and relationship with EPI, and the diagnostic value of quantifying serum concentrations of canine pancreatic specific lipase with the currently available Spec cPL™ assay.

A suspected isolated pancreatic enzyme deficiency should be considered once the more common causes of diarrhea have been ruled out in a puppy or young dog. A partial or complete pancreatic enzyme deficiency should be considered when evaluating a young dog with persistent diarrhea suggestive of EPI, but a normal serum TLI concentration and clinical resolution of diarrhea following PES.

Footnotes

[a] Spec cPL, IDEXX Laboratories, Inc, Westbrook, ME
[b] Viokase-V powder, Fort Dodge Animal Health, Overland Park, KS
[c] *Giardia* ELISA and IFA and *Clostridium perfringens* enterotoxin ELISA, Antech Diagnostics, Oak Brook, IL
[d] Metamucil, Procter & Gamble Co, Cincinnati, OH

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