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Topical Review

Exocrine Pancreatic Insufficiency in the Dog: Historical Background, Diagnosis, and Treatment

Elias Westermarck, DVM, Dipl. ECVIM-CA, PhD, and Maria Wiberg, DVM, PhD

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Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, Finland

Address reprint requests to: Elias Westermarck, DVM, Dipl. ECVIM-CA, PhD, Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, PO Box 57, 00014 University of Helsinki, Finland.

E-mail: elias.westermarck@helsinki.fi.

A B S T R A C T

This overview summarizes research performed during the last decades that has had an impact on the diagnosis and management of exocrine pancreatic insufficiency (EPI) in dogs. Pancreatic acinar atrophy is by far the most common cause for the maldigestion signs of canine EPI. The ability to diagnose pancreatic acinar atrophy in the subclinical phase before the development of total acinar atrophy and manifestation of clinical signs has offered new possibilities to study the pathogenesis of the disease. Diagnosis of exocrine pancreatic dysfunction is based on typical findings in clinical histories and clinical signs and is confirmed with pancreatic function tests. In recent years, the measurement of serum canine trypsin-like immunoreactivity has become the most commonly used pancreatic function test to diagnose canine EPI. Serum trypsin-like immunoreactivity measurement is species- and pancreas-specific. When clinical maldigestion signs of EPI appear, enzyme replacement therapy is indicated. Despite accurate enzyme supplementation, only a small portion of orally administered enzymes are delivered functionally intact into the small intestine. In dogs, the highest enzyme activity in the duodenum has been obtained with nonenteric-coated supplements: raw chopped pancreas or powdered enzymes. Aside from dietary enzyme supplements, dietary changes are often made to improve clinical response, but sometimes weight gain and stool quality remain suboptimal. Other medications for treatment of gastrointestinal tract signs are often used in such dogs with EPI. Antibiotics are the most common adjunctive medication. Of the antibiotics administered, tylosin is used in Finland almost exclusively.

Hardly any organ has been known for so long and yet remained so relatively poorly understood as the pancreas. This puzzling gland and its significance in digestion have concerned the most famous scientists throughout the ages. The one who finally made the breakthrough was Claude Bernard, who published a book in 1856 entitled *Memoir on the Pancreas and on the Role of Pancreatic Juice in Digestive Processes Particularly in the Digestion of Neutral Fat.*[1] Bernard made pancreatic fistulas in dogs, rabbits, and cats, and his experimental results confirmed that fats were emulsified and broken down into fatty acids and glycerol by pancreatic juice. He also concluded from his studies that pancreatic juice is absolutely essential to the absorption of fats, and therefore fatty stools were often a symptom of pancreatic disease. In 1859, Alexander Fles showed for the first time that a human patient with exocrine pancreatic insufficiency (EPI) could be treated by ingestion of raw calf pancreas with every meal.[2]

EPI in Dogs

Exocrine pancreatic function may be diminished by chronic diseases leading to inadequate production of digestive enzymes and classic signs of maldigestion. EPI is a functional diagnosis based on measuring decreased pancreatic secretion capacity by pancreatic function test. The exocrine pancreas has a large reserve secretory capacity, and maldigestion signs are usually not seen until 90% of the secretory capacity is lost. Exocrine pancreatic diseases in dogs that may result in clinical signs of EPI include pancreatic acinar atrophy (PAA), much more rarely by chronic pancreatitis, and very rarely by pancreatic neoplasia.[3-8]

Etiopathogenesis

EPI has been reported in many different breeds, but some breeds appear to be more predisposed than others. EPI is most commonly found in German Shepherds, followed by Rough-coated Collies, Chow Chows, and Cavalier King Charles Spaniels.[5,7,9-12] Female dogs are reported to be overly represented with EPI.[12] The prevalence of the various pancreatic diseases causing clinical signs of EPI is difficult to assess, because pancreatic morphologic examination is needed for the specific diagnosis. However, PAA is reported to be by far the most common cause of severe EPI in dogs. Of all dogs diagnosed with EPI, approximately 50% to 70% were German Shepherds, and in Finland 20% of the cases are found in Rough-coated Collies.[5,11,12] In German Shepherds and Rough-coated Collies, the underlying cause for EPI is essentially always PAA. The estimated prevalence of the disease within these 2 breeds is approximately 1%.[5,10] A similar etiopathogenesis to classical PAA is suspected in other breeds.[12,13]

Pancreatic Acinar Atrophy

The characteristic finding in dogs with PAA is a selective destruction of the digestive enzyme producing acinar cells. Loss of acinar tissue leads to inadequate secretion of pancreatic enzymes and to signs of maldigestion typical of EPI. The endocrine function of the pancreas is usually spared in this process.[3,4,7,14] Canine PAA is a unique disease compared with that in other species. In humans, PAA has been reported but in association with multiorgan diseases such as Sjögren's and Shwachman-Diamond syndromes, associations not recognized in veterinary medicine.[15] Congenital isolated deficiencies in pancreatic enzymes are reported in humans[15] but not in dogs. Experimental studies show that acinar atrophy can be a result of multiple pathogenetic processes involving the exocrine pancreas, such as pancreatic duct obstruction, ischemia, toxicity, nutritional deficiencies or imbalances, and defective secretory and/or trophic stimuli.[8] That said, there is no evidence to support the involvement of these factors in naturally occurring PAA in dogs.[8,16] Congenital exocrine or compound exocrine and endocrine pancreatic hypoplasia in young puppies has

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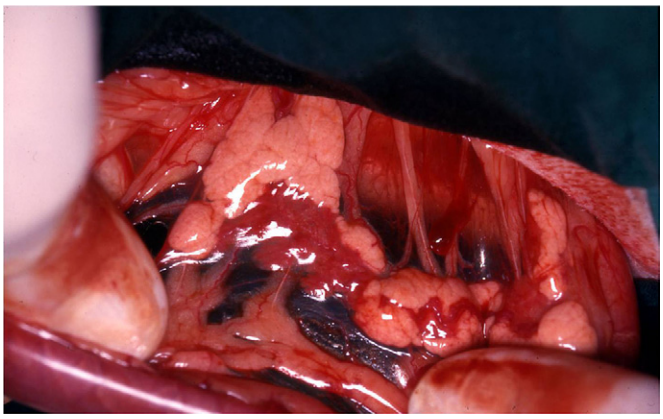

Fig. 1. Dog with subclinical EPI showing a markedly diminished pancreatic mass, including areas of normal glandular structure and areas of tissue having lost its glandular appearance.

been reported.[17-19] Westermarck et al[20] followed the morphologic changes in the pancreas of a German Shepherd puppy bred from parents with PAA. The puppy was born with a grossly and histologically normal pancreas but developed EPI later in life. This finding supports the hypothesis that PAA in this breed is neither hypoplastic nor congenital, but rather an acquired progressive disease process.

The clinical signs of EPI caused by PAA are usually seen in young adults 1 to 4 years of age, although sometimes the clinical disease may develop later in life.[21] The hereditary nature of PAA has been demonstrated in German Shepherds, Rough-coated Collies, and recently in Eurasian dogs. Pedigree analyses suggest that the disease in these 3 breeds is heritable by an autosomal recessive trait.[9,10,13,22,23] Results of a test mating between 2 German Shepherds with PAA showed that only 2 of the 6 offspring were affected, thus suggesting that EPI is not a single-gene disease but rather a polygenic disease.[24]

Recent etiopathogenetic studies showed that PAA in German Shepherds and Rough-coated Collies has some features of autoimmune disease.[25,26] These features include genetic susceptibility to disease and characteristic morphologic and immunologic findings during progression of disease. The ability to diagnose PAA by assay of serum trypsin-like immunoreactivity (TLI) before development of total acinar atrophy and manifestation of clinical maldigestion signs permits the progression to atrophy to be closely monitored.[11] The progression of PAA was divided into a subclinical phase characterized by partial acinar atrophy and a clinical phase with severe end-stage

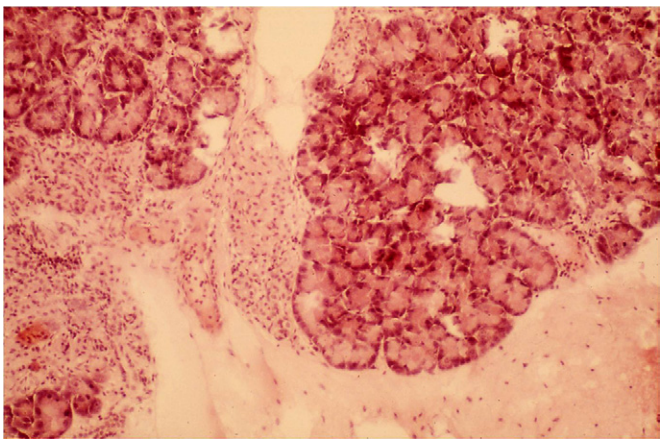

Fig. 2. Exocrine pancreas of a dog with subclinical EPI. Severe mononuclear cell inflammatory reaction is associated with gradual destruction of acinar architecture (border zone active).

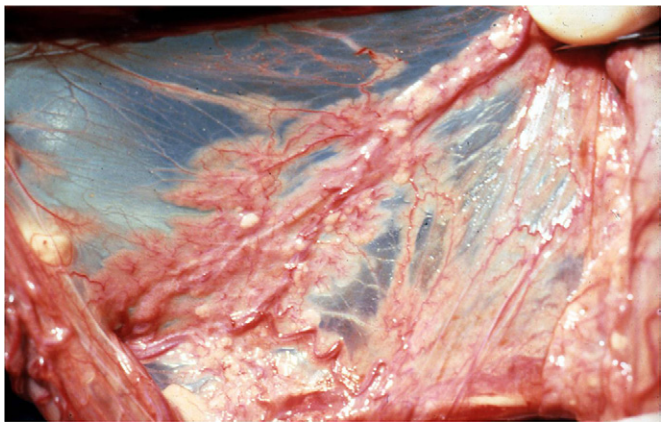

Fig. 3. The duodenal limb of the pancreas of a dog with pancreatic acinar atrophy.

atrophy. In the subclinical phase, both atrophied and normal acinar parenchyma were found. Grossly, the normal pancreatic mass was diminished, and scattered areas of atrophied tissue were found among the normal tissue (Figs. 1 and 2) No hemorrhagic or fibrotic tissue was observed. The histologic findings during the progression of atrophy were typical for an autoimmune disease showing marked lymphocytic inflammation into the partially atrophied acinar parenchyma. Gradual destruction of acinar structure was found in association with the inflammatory reaction. Lymphocytic inflammation was most extensive in the border zones of the normal and affected acinar parenchyma, and lymphocytes spread into the normal acinar parenchyma and intra-acinar areas. As tissue destruction progressed, the findings became more typical of end-stage PAA.[25]

Clinical signs appear only in the end stages of PAA. The gross pathologic findings are typical, showing thin and transparent pancreas with no signs of fibrosis. The normal glandular structure is hardly recognizable and the pancreatic ducts are clearly visible. Histologically, no normal acinar tissue is left in the end stages, or if normal tissue is present, it is found in small, isolated lobuli. The normal acinar parenchyma is replaced by atypical tissue, and ductal structures are prominent. Fibrous tissue is not generally increased, and in some cases the normal tissue is replaced by adipose tissue. Inflammatory cells, lymphocytes, and plasma cells may be found, but in general inflammation is less prominent than in the subclinical phase (Figs. 3 and 4). The endocrine part of the pancreas in dogs with PAA is usually well preserved.[3,7,14,27]

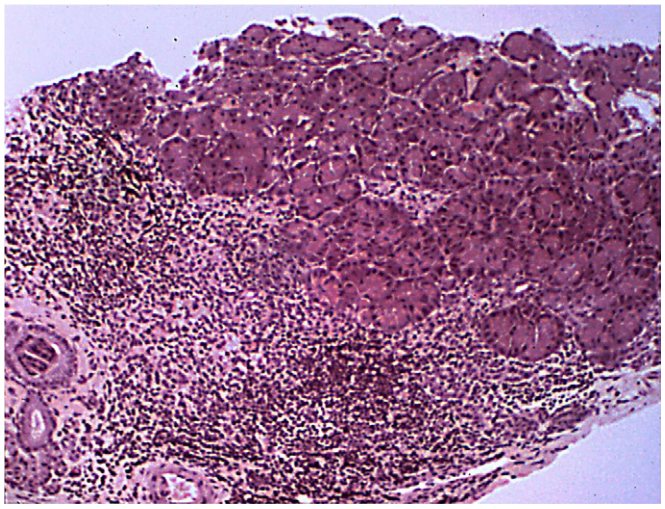

Fig. 4. Pancreas of a dog with clinical EPI, showing typical changes of pancreatic acinar atrophy. Note severe atrophied parenchyma consisting of ductal structures and disorganized cells.