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Topical Review

Exocrine Pancreatic Insufficiency in the Dog: Breed Associations, Nutritional Considerations, and Long-term Outcome

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A B S T R A C T

Canine exocrine pancreatic insufficiency (EPI) is an alimentary tract disorder causing malabsorption and debilitations in affected individuals. This article covers predisposing factors to EPI and response to therapy. Although relatively easy to diagnose, knowledge of breed predispositions (and also of those breeds where the disease is less common) can guide the clinician. Numerous studies have examined therapy for EPI, and a key finding is the variability in response among affected dogs. This implies that close monitoring and individual tailoring of therapy is needed to maximize the chance of success. Important factors affecting outcome are the choice of enzyme preparation, presence of hypocobalaminemia, and the response to the first 2 to 3 months of therapy.

Canine exocrine pancreatic insufficiency (EPI) is an alimentary tract disorder characterized by inadequate production of digestive enzymes from pancreatic acinar cells, leading to the characteristic clinical signs of polyphagia, weight loss, and increased fecal volume.[1-4] This article will first examine signalment factors associated with canine EPI and show how knowledge of such factors can provide an insight into etiopathogenesis. It will next consider therapeutic and nutritional options commonly used by primary care veterinarians, and will finally examine factors associated with favorable response to therapy and long-term remission.

Signalment and Canine EPI

As with any medical disorder, knowledge of associations between certain signalment factors and canine EPI is useful to the clinician. In this respect, when a particular breed is known to be predisposed, diagnostic tests can be prioritized to confirm or eliminate that possibility at the earliest opportunity. Similarly, if a disease were known to be uncommon in particular groups of dog, unnecessary investigations can be avoided with the effect of saving time and expense. In addition to assisting with clinical decision making, knowledge of such associations can also help shed light on possible etiopathogenesis of a disease, and highlight where this may differ among breeds, ages, and genders. The common associations (and lack of associations) between canine EPI and various signalment factors will now be discussed.

Breed Associations

Studies examining breed association and canine EPI have been conducted in North America and Europe. In such studies, a number of breeds have been identified as being at risk for the development of EPI, including Cavalier King Charles Spaniels (CKCS), Chows, Cocker Spaniels, German Shepherd Dogs (GSD), Rough-coated Collies (RCC), and West Highland White Terriers. In one study, EPI in related English setters in Italy has been described, although the exact mechanism was not known.[5] Although these dogs had a congenital form of EPI (absence of acinar cells), the exact mechanism was not known and has never been seen in other dogs of this breed or in other breeds. Therefore, of all the predisposed breeds, the association between GSDs and EPI is well known, with this breed representing ~60% of all cases of EPI.[6,7] In addition, both CKCS and RCC are known to be overrepresented in studies from both North America[7] and Europe.[6]

In a recent European study, a predisposition in Chows was recognized, a finding that had not been identified before.[6] This association may have been identified in this study, but not others, because it was larger in size (~13,000 dogs assessed), such that associations could be identified in even the most uncommon breeds. Indeed, only 38 Chows were tested, but approximately two thirds of those tested were positive. The reasons for such a great prevalence in this breed are not known.

As important as knowledge of predispositions is a need to recognize where the disease may be underrepresented, and one study has examined such "negative" associations.[6] Observed prevalence in Boxers, Great Danes, Golden retrievers, Labrador retrievers, Rottweilers, and Weimaraners was significantly less, most notably in Boxers in which, of 524 individuals tested, none had EPI. However, EPI has been documented in Boxers in North America,[7] although that study did not specifically examine the issue of underrepresen-

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tation of breeds. Nonetheless, genetic differences may account for the difference in prevalence in EPI in dogs from different continents.

Gender

In most studies conducted to date, female dogs are overrepresented compared with male dogs. Although this female association is typical of most breeds, including Chows, CKCS, and GSD, it is less clear cut for RCC where it has been shown in some[8,9] but not all[6] studies.

Age

Onset of EPI typically arises in young adult animals (median age 3 years),[2-4,6,10] although cases range from growing dogs (3 months and up) to those in late adulthood and even geriatric (e.g., 17 years age).[6] Interestingly, median age of onset varies among breeds, with cases in GSDs and RCC occurring, on average, at a younger age (median 3 years) than CKCS (median age 7 years). Of all breeds affected, dogs of the Chow groups are youngest (median age 18 months). This may imply differences in pathogenesis among different breeds (see below).

Differences in Signalment and Differences in Pathogenesis of EPI in Different Dog Populations

As mentioned above, various breeds are predisposed to EPI, but can be separated into 2 distinct groups depending on age of onset. Age of onset can provide clues to the likely pathologic mechanisms: in breeds with early-onset disease an immune-mediated mechanism is possible or the disease may be congenital, whereas breeds in which EPI manifests later might develop the disease through other mechanisms including chronic pancreatitis.

Onset of EPI occurs at a relatively young age in GSD and RCC, and pancreatic acinar atrophy (PAA) is reportedly the most common cause. The disease may, in fact, have an immune-mediated pathogenesis, as evidenced by the presence of lymphoplasmacytic infiltrates in the pancreas of dogs of these breeds with subclinical EPI.[8,9] This age of onset is similar to that seen for other immune-mediated glandular diseases such as steroid-responsive meningitis and immune-mediated polyarthritis.[11] Although some studies have suggested that the disease is inherited in an autosomal recessive manner in both breeds,[8,9,12-16] this is at odds with the female predisposition. Furthermore, other studies have questioned the proposed autosomal recessive inheritance mechanisms and a single causal gene has not been identified despite numerous attempts,[17] and the fact that recent studies have questioned the pattern of autosomal recessive inheritance.[18] Further work is therefore required to ascertain the exact etiopathogenesis. Chows also tend to be diagnosed with EPI at a relatively young age, again arguing for a similar mechanism in this breed. However, no work has been conducted on pathogenesis in this breed and, alternative mechanisms, including congenital disorders such as pancreatic hypoplasia, would also be possible.[3]

In contrast to the GSD and RCC breeds, EPI cases develop later in life for the CKCS breed,[6] implying that a different pathogenetic mechanism might be responsible in such cases. Other than PAA, proposed pathologic mechanisms leading to onset of EPI include chronic pancreatitis (CP), pancreatic hypoplasia, and pancreatic neoplasia.[2,3] Of all such possibilities, CP is most likely because CKCS are reportedly predisposed and, therefore, ongoing uncontrolled pancreatic inflammation is the reason that they develop EPI. CP is also a common cause of EPI in cats and human beings, and most frequently arises in middle age onward, a pattern mirroring what is seen for dogs.[19-21] Because CP can be notoriously difficult to diagnose,[22,23] it is, perhaps, not surprising, that EPI cases do not commonly have a history of gastrointestinal disease before onset in this breed.[24]

Of all breeds known to be underrepresented, the most interesting is the Boxer, especially in light of the fact that a decreased prevalence for diabetes mellitus is also reported in this breed.[25] The decreased observed prevalence for both an exocrine and an endocrine pancreatic disease condition in Boxers is remarkable, although the underlying mechanism requires further study. One possible explanation is that the exocrine and endocrine pancreas of the Boxer is more able to withstand injury than that of other breeds; this could result from decreased predisposition to immune damage, decreased cell death during disease or more robust intrinsic regenerative mechanisms. Candidate proteins could include the regenerating (*reg*) proteins. In humans and rodents, *reg* proteins are secreted in pancreatic juice and may be protective of both exocrine and endocrine tissue.[26] Furthermore, in humans, overexpression of *reg* has been noted in some forms of cancer,[26] noteworthy, because Boxers are a breed prone to neoplasia.[24,27] However, to date, *reg* proteins have not been identified in any breed of dog, and further study is required to determine whether they, or other proteins, may have a role to play in protection from pancreatic injury or neoplasia in this species.

Finally, the reason for the gender association is not yet known but, as mentioned above, has enabled reappraisal of the possible genetic mechanisms underlying EPI.

Nutritional and Therapeutic Considerations

Pancreatic Enzyme Replacement

Various therapies are used for dogs with EPI, but by far the most important is pancreatic enzyme replacement, although cases have reportedly been maintained for prolonged periods without supplementation.[28,29] A range of products have been recommended including enteric-coated preparations (including tablets, capsules, and granules), uncoated enzyme powder, and raw pancreas. In a recent study assessing prescribing habits of UK veterinarians, approximately two thirds gave uncoated preparations, whereas most of the rest gave a coated preparation and only a minority ($< 1\%$) gave raw pancreas.[28] The findings of this study contrasted with those of an earlier UK study, whereby only one third gave uncoated preparations.[10] There has been considerable debate about efficacy of such products, with earlier work suggesting that dogs given uncoated enzymes had a better response to therapy,[10] but more recent work has not shown such a difference.[28] In light of this, a recent blinded randomized controlled trial (RCT) was conducted by the author and colleagues, comparing efficacy of an enzyme supplement with and without an enteric coating. Although signs of diarrhea, flatulence, and appetite change were not noticeably different, use of an enteric coating improved weight gain compared with the uncoated product (unpublished observations of the author). This suggests that, despite the initial work, the use of products with an enteric coating may convey a treatment advantage for canine EPI. Of course, different enteric-coated products may vary in efficacy, such that these findings are not necessarily applicable to other preparations. Further, the improved efficacy could be overcome by using a higher dose of uncoated enzyme, although this could lead to a delayed response and increase the cost of long-term therapy, and both factors can be reasons for euthanasia of dogs with EPI (see below).

Dietary Modification

The historical approach for dietary manipulation in canine EPI is to switch to a fat-restricted diet on the basis that fat digestion is dependent on pancreatic lipase, and normal digestion cannot be achieved even with enzyme replacement therapy.[29-31] Further, in an experimental model of EPI, such a strategy can improve fat assimilation.[32] It is also suggested to improve resolution of clinical signs, thereby improving patient demeanor.[30] However, such a strategy suffers from the problem that, on such a calorie-restricted ration, it may be difficult