Subclinical exocrine pancreatic insufficiency in dogs

Maria E. Wiberg, DVM, and Elias Westermarck, DVM, PhD

Objective—To study progression of autoimmune-mediated atrophic lymphocytic pancreatitis from the subclinical to the clinical phase (exocrine pancreatic insufficiency [EPI]) and determine whether progression of the disease could be halted by treatment with immunosuppressive drugs.

Design—Randomized controlled trial.

Animals—20 dogs with subclinical EPI.

Procedure—Diagnosis of subclinical EPI was determined on the basis of repeatedly low serum trypsin-like immunoreactivity (TLI) in dogs with no signs of EPI. Laparotomy was performed on 12 dogs with partial acinar atrophy and atrophic lymphocytic pancreatitis. A treatment group (7 dogs) received an immunosuppressive drug (azathioprine) for 9 to 18 months, and a non-treatment group (13) received no medication.

Results—During the subclinical phase, serum TLI was repeatedly low (<5.0 µg/L). Although a few dogs had nonspecific gastrointestinal tract signs, they did not need diet supplementation with enzymes. While receiving immunosuppressive medication, treated dogs had no clinical signs of EPI, but within 2 to 6 months after treatment was stopped, 2 dogs had signs of EPI, and diet supplementation with enzymes was started. Five of the 13 untreated dogs needed diet supplementation with enzymes within 6 to 46 months. During follow-up of 1 to 6 years, 3 of the 7 treated dogs and 8 of the 13 untreated dogs did not need continuous diet supplementation with enzymes.

Conclusions and Clinical Relevance—Progression of atrophic lymphocytic pancreatitis varied widely. The subclinical phase may last for years and sometimes for life. The value of early treatment with an immunosuppressive drug was questionable and, because of the slow natural progression of the disease, cannot be recommended. (J Am Vet Med Assoc 2002;220:1183–1187)

Results of recent etiopathologic studies of exocrine pancreatic insufficiency (EPI) in German Shepherd Dogs and rough-coated Collies indicate that the disease is a result of autoimmune-mediated atrophic lymphocytic pancreatitis. Autoimmune pancreatitis leads to destruction and atrophy of pancreatic acinar tissue and diminished secretion of digestive enzymes. Cellular mechanisms have a major role in the pathogenesis of this disease, because the gradual destruction of acinar parenchyma is associated with marked infiltrative inflammation by T lymphocytes.

Subclinical and clinical phases of EPI can be recognized. The term subclinical EPI (SEPI) is used when the pancreas has sufficient reserve secretory capacity to prevent maldigestion, which is a clinical sign of EPI. Pathologic findings in the subclinical stage are typical of partial acinar atrophy, with diminished normal pancreatic tissue and scattered areas of partially destroyed and atrophied parenchyma. Consistently low serum trypsin-like immunoreactivity (TLI: <5.0 µg/L; reference range, >5.0 to 35.0 µg/L) is diagnostic for SEPI and partial acinar atrophy. In the clinical phase of EPI, the autoimmune process leads to almost total destruction of acinar parenchyma and to pathologic findings typical of severe pancreatic acinar atrophy.

Typical signs of EPI (polyphagia, weight loss, and soft voluminous feces) associated with abnormal low serum TLI (<2.5 µg/L) are found.

Until now, the questions of whether atrophic lymphocytic pancreatitis will always lead to clinical manifestations of EPI and whether it is possible to prevent the clinical disease have been unanswered. Although prognosis of EPI is considered to be good, about a fifth of dogs are euthanatized because of poor treatment response or because the owners refuse to continue lifelong and expensive dietary enzyme supplementation. Immunosuppression is a potential treatment objective in autoimmune diseases. For successful immunosuppressive treatment, it is essential to initiate treatment while some reserve functional capacity still exists and before clinical signs of the disease appear. Stimulation of the pancreas of dogs with SEPI by use of enterohormones causes low serum TLI to increase to the reference range, but in the clinical phase, no response to enterohormonal stimulation is found.

The purpose of the study reported here was to determine whether atrophic lymphocytic pancreatitis invariably leads to the clinical phase of EPI and whether progression of the disease could be halted by treatment with immunosuppressive drugs.

Materials and Methods

Treatment group—The treatment group comprised 6 German Shepherd Dogs and 1 rough-coated Collie. Four dogs were male, and 3 were female; ages ranged from 1 to 6 years (median, 2 years). The diagnosis of SEPI was made on the basis of repeatedly low serum TLI (<5.0 µg/L) in dogs that were healthy and had no clinical signs of EPI (polyphagia, weight loss, and soft voluminous feces), and partial acinar atrophy was confirmed by use of pancreatic biopsy in all dogs. Median serum TLI for 7 dogs at the time of laparotomy was 2.0 µg/L (range, 1.0 to 3.3 µg/L). Reference range for serum TLI has been reported as 5.2 to 34.0 µg/L. Treatment was started with a combination of prednisone (1.0 mg/kg [0.45 mg/lb], q 24 h for 1 week, then tapered over 2 to 3 weeks) and azathioprine (1.5 to 2.0 mg/kg [0.7 to 0.9 mg/lb], q 24 h for 3 to 4 weeks) and then continued with the same dosage of azathioprine every other day for 9 to 18 months (median, 12 months).
Non-treatment group—The non-treatment group comprised 11 German Shepherd Dogs and 2 rough-coated Collies. Seven dogs were male, and 6 were female; ages ranged from 2 to 8 years (median, 4 years). For 8 dogs, diagnosis of SEPI was confirmed on the basis of clinical appearance of health with no clinical signs of EPI and 2 consecutive serum TLI values < 5.0 μg/L. For 5 dogs, partial acinar atrophy was confirmed by use of laparotomy and pancreatic biopsy. Median serum TLI at time of diagnosis was 2.7 μg/L (range, 1.5 to 4.1 μg/L), which was significantly (P < 0.05) greater than that of the treated dogs. Untreated dogs received no continuous treatment during the follow-up period. The study plan was approved by the Ethical Committee of Veterinary Faculty, Helsinki University, and owners gave informed consent.

TLI measurements—During the follow-up period, repeated clinical examinations, hematologic and serum biochemical measurements, serum TLI measurements, TLI stimulation tests (TST), and telephone interviews with owners were performed for all dogs. Serum TLI was measured by use of radioimmunoprecipitation after withholding food overnight. For TST, the first serum sample for TLI measurement was taken after food was withheld overnight. The pancreas was stimulated by use of IV infusion of secretin (1.0 U/kg [0.45 U/lb]) and cholecystokinin (1.0 U/kg) during a 1- to 2-minute period. The second serum sample for TLI measurement was collected 20 minutes after stimulation. Histologic examination—Laparotomy and pancreatic biopsy were performed as described. In 3 of the 7 treated dogs, pancreatic biopsy was repeated at the end of the treatment period by use of laparotomy. At the end of 4 years of treatment, pancreatic tissues were obtained from 1 dog at necropsy. For untreated dogs, pancreatic tissues were obtained at necropsy from 1 dog after 4 years of follow-up. Pancreatic specimens were fixed in neutral-buffered 10% formalin and routinely processed for histologic examination.

Statistical analysis—The Wilcoxon signed rank test was used to study the significance of the response to the TST in the treated and non-treated group. Differences between groups for TST and TLI results were evaluated by use of the Mann-Whitney U test. A value of P < 0.05 was considered significant.

Results

Treatment group—Total follow-up period ranged from 13 to 74 months (median, 17 months). Before treatment was initiated, the dogs were clinically normal and did not have chronic clinical signs of gastrointestinal tract abnormalities. Clinical gastrointestinal tract signs that were not typical of EPI (eg, occasional diarrhea or borborygmus) were detected in 2 of 7 dogs; in 1 dog, the clinical signs were self-limiting, and another dog responded when its diet was changed (details unknown).

During treatment, the general health of the dogs was similar to that before treatment, and treatment was well tolerated. In 1 dog, increased liver enzyme activities were detected 4 weeks after administration of azathioprine. When treatment was discontinued for 2 weeks, values returned to reference ranges, and treatment was continued without further difficulties.

After the treatment period, clinical signs of EPI (polyphagia, weight loss, soft voluminous feces) appeared in 2 dogs within 2 and 6 months, respectively. The clinical signs appeared rapidly and were associated with decreased serum TLI (before treatment, 1.5 and 2.5 μg/L; after treatment, 0.6 and 1.9 μg/L). Both dogs responded to enzyme replacement therapy.

One dog had increased clinical signs after treatment, but serum TLI had not decreased. The dog responded to treatment with prednisone but was excluded from further follow-up because of the treatment. Another dog was euthanatized for an unrelated reason after treatment concluded. Three dogs remained in the subclinical phase and did not require enzyme treatment during the entire follow-up period (median, 71 months; range, 44 to 74 months). One dog was euthanatized after 6 years of follow-up.

A second pancreatic biopsy was performed on 4 of 7 dogs at the end of treatment. In all dogs, gross and histologic findings were similar to those at time of diagnosis. Grossly, the amount of healthy pancreatic tissue appeared to be the same as or less than before treatment. Healthy pancreatic tissue was scant, but normal glandular structures were found among the atrophied tissue. Histologically, infiltration of lymphocytes was evident. Severity of histologic findings was not compared between biopsy specimens obtained before and after treatment because of the patchy changes in the pancreas. In 1 dog that was euthanized and necropsied after 4 years of treatment, increased acinar atrophy was found along with some unaffected pancreatic tissue. The dog had no clinical signs of EPI.

Non-treatment group—Total follow-up period ranged from 6 to 46 months (median, 24 months). In general, the dogs were healthy and had no need of continuous diet supplementation with enzymes. Four of 13 dogs had occasional gastrointestinal tract problems not typical of EPI, and all dogs responded when their diet was changed to another unspecific diet.

During the follow-up period, dietary enzyme supplementation was instituted in 5 of the 13 dogs. Three dogs developed clinical signs of EPI in 13 to 46 months. The clinical signs appeared rapidly and were associated with TLI of 0.8 and 1.8 μg/L in 2 dogs. One of these dogs was euthanatized after appearance of clinical signs. Examination of the pancreas revealed progression from partial acinar atrophy to severe acinar atrophy; within atrophied parenchyma, some sparse areas of normal tissue were found.

In 2 dogs, nonspecific chronic gastrointestinal tract abnormalities appeared after 6 and 12 months of follow-up and were associated with TLI of 1.8 and 2.2 μg/L, respectively. Dietary supplementation with enzymes yielded a good response.

Eight of 13 dogs did not have clinical signs of EPI and did not need enzymes within 12 to 44 months (median, 33.5 months) of follow-up. One dog was euthanatized at 11 years of age with > 3 years of follow-up and no clinical signs of EPI.

Serum TLI measurements—During the subclinical phase of follow-up, serum TLI measurements were obtained in treated dogs 5 to 16 times (median, 9 times) and from untreated dogs 3 to 8 times (median, 5 times).
Median serum TLI for all dogs was <5.0 µg/L (treated dogs, 2.6 µg/L [range, 1.5 to 3.4 µg/L]; untreated dogs, 2.5 µg/L [range, 1.2 to 4.6 µg/L]). In treated and untreated dogs, single TLI concentrations ranged from 0.5 to 8.2 µg/L and 0.5 to 9.4 µg/L, respectively. Single serum TLI concentrations within reference range were found during the azathioprine treatment period in 2 dogs and after treatment in 2 dogs. In the untreated dogs, single TLI concentrations >5.0 µg/L were found in 4 of 13 dogs. No associations among single serum TLI values >5.0 µg/L, changes in clinical signs, or increases in serum amylase and lipase activities were detected. During the subclinical phase, mean serum TLI in 7 dogs (2 in the treated group, 5 in the nontreated group) that subsequently developed clinical EPI (median concentration, 2.5 µg/L; range, 1.2 to 4.1 µg/L) were not significantly different, compared with those of the 13 dogs that remained in the subclinical phase and did not need continuous diet supplementation with enzymes during the follow-up period (median concentration, 2.6 µg/L; range, 1.9 to 4.6 µg/L). At the time of development of clinical signs of EPI (n = 6), mean serum TLI was 1.8 µg/L (range, 0.6 to 2.2 µg/L).

Serum TST—During the subclinical phase of the follow-up period, serum TST were performed on the 7 treated dogs 3 to 10 times (median, 6 times) and on 8 untreated dogs 1 to 4 times (median, 2.5 times). After stimulation with enterohormones, median TLI concentration was increased in treated dogs from 2.6 µg/L (range, 1.8 to 6.0 µg/L) to 13.6 µg/L (range, 4.2 to 46.2; P < 0.05) and in untreated dogs from 2.5 µg/L (range, 1.0 to 4.6 µg/L) to 5.8 µg/L (range, 1.9 to 50 µg/L; P < 0.05). Low serum TLI increased to reference range in 6 of the 7 treated dogs and in 5 of the 8 untreated dogs. Response varied among dogs and among repeated measurements in individual dogs.

During the subclinical phase of total follow-up, median TLI in response to TST was 3.3 µg/L (range, 0.9 to 8.1 µg/L) in the 4 dogs that subsequently developed clinical EPI and 18.8 µg/L (range, 0.8 to 46.9 µg/L) in 6 dogs that remained in the subclinical phase. These results were not significantly different (dogs with results of at least 3 TST were included).

Discussion

In German Shepherd Dogs and rough-coated Collies, EPI is the result of autoimmune-mediated atrophic lymphocytic pancreatitis.13 Results of the study reported here indicated that progression from the subclinical to the clinical phase of EPI can vary markedly. The autoimmune process may lead to severe atrophy of acinar tissue and signs of malabsorption within a short period, or the disease may remain in the subclinical phase for years, possibly for life. Despite partial acinar atrophy, the reserve secretory capacity of the pancreas prevents the appearance of clinical signs of EPI in the subclinical phase. Of the 20 dogs included in this study, 11 did not need continuous enzyme administration during the long-term follow-up period of 1 to 6 years.

The ability to diagnose pancreatic acinar atrophy in the subclinical phase raised the question of whether it is possible to stop the autoimmune-mediated destruction of acinar tissue and thus prevent the appearance of clinical signs. Results of a previous study9 in 1 dog revealed that atrophy could develop in a short period. In autoimmune diseases, it is essential to start treatment with immunosuppressive drugs before total loss of functional capacity.14 With pancreatic acinar atrophy, this means starting the treatment before clinical signs appear.

In the study reported here, treatment in the subclinical phase was started with a combination of prednisone and azathioprine and then continued by administration of azathioprine every other day. Cortisone has been reported to be effective in treatment of a new model of pancreatitis in humans, with features of an autoimmune disease.14,15 Azathioprine is commonly used in the treatment of immune-mediated diseases, and reported adverse effects are rare. It is especially effective in treatment of T-cell-mediated diseases.16-20 The treatment protocol used in our study was well tolerated, and no severe adverse effects, including bone marrow suppression and acute pancreatitis,19,20 were identified.

The goal of successful treatment is to stop or slow the autoimmune process.12 On the basis of the outcome in our treatment group, treatment may have prevented the appearance of clinical signs. However, soon after treatment was discontinued, 2 of 7 dogs developed clinical EPI, indicating that the treatment was not able to prevent progress of the autoimmune process in these dogs. After 2 to 4 years of treatment, the disease in 3 dogs in the treated group remained subclinical. In contrast, 5 of 13 dogs in the nontreated group developed clinical signs of EPI, 1 after 4 years in the subclinical phase. Our conclusion is that because the natural progress of the disease seems to be quite variable, the role of treatment in slowing acinar atrophy was difficult to assess and remains uncertain. We do not presently consider long-term treatment in the subclinical phase as a rational option, because the prognosis of clinical EPI with dietary enzyme supplementation is generally satisfactory.

We were unable to explain why progression of the disease in individual dogs differed. The speed of disease progression and the degree of organ dysfunction may vary, which is typical of many autoimmune diseases. The disease may either develop rapidly or remain at a standstill, depending on the presence or absence of triggering environmental factors.22-24 These triggering factors are usually difficult to identify, and, therefore, their role in many autoimmune diseases is speculative. It is not presently known which environmental factors are involved in the pathogenesis of atrophic lymphocytic pancreatitis in dogs. Only a few attempts have been made to study possible predisposing factors, and none have been identified.5

Repeatedly low serum TLI (<5.0 µg/L) is essential in diagnosing SEPI and partial acinar atrophy.6 In our study, diagnosis of SEPI was made in 8 dogs only on the basis of repeated TLI measurements; 3 of these dogs subsequently developed clinical EPI. Long-term
follow-up also revealed the importance of repeating TLI measurements when subclinical disease is suspected. Although median serum TLI during the follow-up period remained < 5.0 µg/L in all dogs, single TLI values within the reference range were detected in a few dogs. High serum TLI in patients with pancreatic dysfunction may be the result of acute inflammatory attacks in the residual pancreatic tissue.23-25 We occasionally found increased TLI during azathioprine treatment and after the treatment period, as well as in dogs that received no treatment. Because these exceptional values were still within reference range and were not associated with any changes in clinical signs or increases in serum amylase or lipase activities, they were not considered to be indicators of acute pancreatitis. Moreover, because atrophic lymphocytic pancreatitis is a gradually progressive disease, dogs with subclinical disease may have TLI within reference range, especially when an indirect pancreatic function test is used for diagnosis.

In our study, we were able to further assess the prognostic value of single serum TLI measurements and the TST. Although TLI reflects the amount of remaining pancreatic mass,28 repeated measurements were not found to be helpful in predicting progression of the disease. In some dogs with subclinical disease, serum TLI was as low as in dogs with clinical EPI long before these dogs had any signs of maldigestion. Furthermore, during the follow-up period, serum TLI of individual dogs had fluctuations that made assessment of the predictive value of the measurement more difficult.

The TST has been suggested to have predictive value greater than that of single TLI measurements.5 Although dogs in the subclinical phase did usually have no response to stimulation with enterohormones, no response was apparent in the severe clinical phase.6 We were able to perform repeated TST in dogs with subclinical EPI, but results were disappointing. In the subclinical phase, low serum TLI usually increased into the reference range, and a significant difference between values obtained before and after TST was detected. However, the degree of response varied among dogs and within the same dog with repeated testing. No progressively decreased responses were found in those dogs that later developed clinical EPI.

As reported, neither the serum TLI nor the response to TST will determine whether enzyme replacement treatment is needed; instead, test results must be in agreement with clinical signs.6,29 When abnormally low serum TLI (< 2.5 µg/L) is associated with maldigestion typical of EPI, the treatment of choice is dietary enzyme supplementation. Diagnosis may be difficult when serum TLI is < 5.0 µg/L and the dog has intermittent or chronic gastrointestinal tract signs not typical of EPI; whether the signs are attributable to subnormal pancreatic function, underlying small intestinal disease, or a combination thereof is the dilemma. A few dogs in our study had intermittent nonspecific gastrointestinal tract signs that were managed with dietary modification. During long-term follow-up, 3 dogs developed severe chronic gastrointestinal tract signs that were not typical of EPI. One of these dogs was treated with cortisone. The other 2 dogs received trial treatment with enzymes and had a good response. For dogs such as these, we recommend diagnostic tests and treatment for underlying small intestinal disease, if present; if test results are negative or treatment response is poor, trial treatment with enzymes is indicated.

References

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