Elevated serum creatinine and hyponatraemia as prognostic factors in canine acute pancreatitis

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ABSTRACT

Objective To evaluate prognostic factors for canine acute pancreatitis (AP) based on clinical and laboratory data that can be easily assessed in veterinary practice.

Design Retrospective study between January 2010 and December 2013.

Methods The diagnosis of AP was based on clinical signs and an abnormal SNAP® cPL™ test result, concurrently with an ultrasound pattern suggestive of pancreatitis. Dogs were divided into survivors and non-survivors. We evaluated 12 clinical and laboratory parameters: respiratory rate, rectal temperature, white blood cells, haematocrit, total serum proteins, albumin, creatinine, cholesterol, total and ionised calcium, sodium and potassium. Clinical and clinicopathological data were statistically compared between survivors and non-survivors. A value of $P < 0.05$ was considered significant and $P < 0.01$ as highly significant. The odds ratio (OR) was calculated.

Results The study enrolled 50 client-owned dogs with a diagnosis of AP. Serum creatinine ($P = 0.017$) and sodium ($P = 0.004$) correlated significantly with the outcome. Serum sodium < 139.0 mmol/L (139.0 mEq/L) and serum creatinine > 212 μmol/L (2.4 mg/dL) were associated significantly with poor prognosis. Azotaemia (OR 12.5; 95% confidence interval (CI) 1.32–118.48) and hyponatraemia (OR 4.9; 95% CI 1.36–17.64) were associated with increased risk of death.

Conclusions In dogs with AP, hyponatraemia and azotaemia seem to be significantly associated with an increased risk of death.

Introduction

in veterinary medicine, acute pancreatitis (AP) is a relatively frequent pathological condition. Although AP is generally regarded as a significant illness in dogs, its actual incidence is unknown. Some dogs have subclinical

or mild disease and recover within a few days without specific treatment. However, others show more severe forms, which may result in death if not promptly recognised and treated.[1,2] An early assessment of disease severity and the identification of risk factors, is thus essential for the appropriate management of AP.[2]

Scoring systems based on the careful monitoring of patients in an intensive care unit are commonly used in human medicine.[3–6] The acute physiology and chronic health evaluation system (APACHE) is considered as the most sensitive model, able to make prognosis within the first 24 h, with an accuracy of 90%. Clinical parameters included in the APACHE classification system are body temperature, mean arterial pressure, heart and respiratory rates, oxygen partial pressure, arterial pH, sodium and potassium ions, serum creatinine, haematocrit (Hct) and white blood cells (WBC).[7]

In veterinary medicine, two recent studies evaluated the prognosis and outcome of AP in dogs. Mansfield et al.[8] developed a clinical severity index to report the outcome in dogs with an ultrasound or histological diagnosis of AP. An elevated clinical severity index score was associated with higher mortality rate.

Another study found that hypothermia and metabolic acidosis correlated significantly with poor prognosis.[2]

The aim of the present study was to evaluate the prognostic factors for canine AP based exclusively on clinical and laboratory data that can be easily assessed in veterinary practice.

Materials and methods

For the present study, an evaluation of the database of all dogs admitted to the University of Pisa Veterinary Teaching Hospital between January 2010 and December 2013 was performed in order to identify dogs with AP. The diagnosis of AP was based on the following criteria: (1) ≥ 2 of the following clinical signs: abdominal pain, polyuria/polydipsia, diarrhoea, vomiting or anorexia/dysorexia for fewer than 7 days, (2) ultrasound evidence of AP (Xario XG ultrasound unit, Toshiba, Tokyo, Japan) without other identifiable diseases and (3) abnormal SNAP® cPL™ test (Idexx Laboratories, Milan, Italy).

Ultrasound findings associated with pancreatic inflammation vary with the severity and chronicity of the disease. Decreased echogenicity in AP reflects oedema, haemorrhage and necrosis, while the surrounding fat is generally moderately hyperechoic. When significantly enlarged, the right lobe of the pancreas may move from its normal position, dorsal or dorsomedial to the duodenum, to lie dorsolaterally. The stomach or duodenum may become distended with fluid, showing wall thickening and lack of peristalsis, because of

functional ileus. Changes in the pancreas may be accompanied by localised or generalised accumulation of peritoneal effusion. Severe pancreatitis can also result in generalised peritoneal effusion. The pancreatic duct may be dilated and become as wide as the pancreatic-duodenal vein.[9]

Dogs were included in the study if data for the following 12 para- meters were available: respiratory rate, rectal temperature, WBC, Hct, total serum proteins, albumin, creatinine, cholesterol, total and ionic calcium, sodium and potassium (Table 1). Complete blood count (Procyte DX, Idexx Laboratories), serum biochemis- try profile (Liasys, Assel srl, Guidonia-Montecelio, Rome, Italy) and electrolytes (Stat Profile pHOx Series Analyzers, Nova Bio- medical, MA, USA) were performed by automated clinical analysers.

The following were exclusions from the study: previous diagnosis of AP, chronic kidney disease, diabetes mellitus, hypothyroidism, hypoadrenocorticism, hyperadrenocorticism or pancreatic neoplasia.

Dogs were divided in two groups: survivors and non-survivors. Non- survivors included dogs that had died within 7 days of hospital admission. Clinical and clinicopathological data were compared between survivors and non-survivors. Cut-off values for serum creatinine and sodium were taken from the highest values in the survivor group. Table 2 shows the cut-off values of serum sodium < 139.0 mmol/L (139.0 mEq/L), and serum creatinine > 212 μmol/L (2.4 mg/dL). Odds ratio (OR) was calculated using these cut-off values. Data were analysed with the Mann- Whitney test using Statgraphics Plus 5.1 (Manugistic Inc., Rockville, MD, USA). A value of $P < 0.05$ was considered significant and $P < 0.01$ as highly significant.

Results

The study included 48 dogs (20 males, (18 intact, 2 neutered), 28 females, (19 intact, 9 spayed)) of several breeds. The mean age was 9.2±3.8 years.

The most commonly involved breeds were mixed breeds (14 dogs), Dachshund (3), Beagle (3), Siberian Husky (3), Yorkshire Terrier (3), Boxer (2), Labrador Retriever (2), German Shepherd (2), English Set- ter (2) and 1 each of 14 other breeds.

At clinical examination 43/48 dogs (89.6%) showed depression, anorexia/dysorexia, weight loss, nausea or vomiting and diarrhoea. In addition to clinical signs of AP, 3 patients (6.2%) had respiratory dis- tress, 1 patient had ascites (2%), 1 had jaundice and 1 had hypovolaemic shock.

Table 1 reports the reference range, mean value and standard deviation for the 12 clinical and laboratory parameters. Of the 48 dogs, 17 (35.4%) died within the first 48 h. Serum creatinine and sodium levels were statistically associated with outcome in these canine cases of AP: P = 0.017 and P = 0.004, respectively (Table 1). The remaining parameters (respiratory rate, temperature, Hct, WBC, total protein, albumin, cholesterol, total calcium, calcium and potassium) did not show a significant difference between the survivor and non-survivor groups. The presence of a left shift in the neutrophil count was present in 13 dogs (27%), but was not associated with the outcome. Azotemia (OR 12.5; CI 1.32– 118.48) and hyponatremia (OR 4.9; CI 1.36–17.64) were associated with an increased risk of death.

Discussion

This study concurrently used clinical signs (anorexia, lethargy, abdominal pain, vomiting), ultrasound findings and abnormal SNAP® cPLTM test results as inclusion criteria for canine AP, as reported in a recent work.[10]

The SNAP® cPLTM test is considered to be the most sensitive and specific marker of AP in dogs.[11,12] To the best of our knowledge, only one research group has simultaneously used the SNAP® cPLTM test, abdominal ultrasound and clinicopathological findings as inclusion criteria for AP.[10]

Others have shown that the SNAP® cPLTM agrees with the Spec cPL test: 96–100% in normal canine serum samples with normal levels of canine pancreatic lipase (cPL) and 88–92% for samples with an elevated cPL.[13]

In the study by Pápa et al., a diagnosis of AP was based on the simultaneous presence of clinical signs of AP, increased activity of serum amylase or lipase, ultrasonographic and/or macroscopic appearance and cytological or histological evidence of AP.[2] Serum amylase and lipase have been reported to have a low sensitivity (50% and 71%, respectively[11]) and low specificity (50% and 43%, respec- tively[11]). However, in 2008, Steiner et al. showed no correlation between elevated levels of lipase or amylase and canine AP.[14]

Mansfield et al. proposed a clinical severity index for canine AP.[8] The diagnosis of AP was made on the basis of an abdominal ultra- sound or histological examination. Although abdominal ultrasound is reported to have a moderate sensitivity (68%[15]), no clear data are available regarding specificity.

However, abdominal ultrasound alone, based on purely morphologi- cal criteria, cannot unequivocally identify a mild or recent inflamma- tory condition in which anatomical changes have not yet occurred.[1,9,16] Although pancreatic biopsy and histopathological examination are the best options for a diagnosis of AP, they still have a limited feasibility in clinical practice.[1,14]

A recent study, performed in dogs with clinical signs of acute abdominal disease (≥ 2 of the following clinical signs: acute (< 2 days) onset of abdominal pain, vomiting, abdominal distension or diarrhoea), highlighted the sensitivity (82%) and specificity (59%) of the SNAP® cPLTM test.[17] Therefore, a positive SNAP® cPLTM test result may provide a 'false positive' diagnosis for AP in up to 40% of dogs presenting with abdominal pain.[17] The specificity of the SNAP® cPLTM test decreased to 45% in dogs with hyperadrenocorticism, which showed abnormal results, without clinical signs suggestive of AP.[18] The inclusion criteria and the use of multiple diagnostic modalities may have increased the significance of the results in the present study.

It would be useful to identify a wide range of prognostic factors, pos- sibly including clinical signs and laboratory parameters commonly altered during canine AP.[1,16,19] In the present study, the choice of 12 variables was based on the physiopathological mechanisms that occur during canine AP: respiratory rate, rectal temperature, WBC, total serum protein and serum albumin are influenced by the magni- tude of the inflammation; serum creatinine concentration is associ- ated with various degrees of hydration and, possibly, with prerenal azotaemia; lower total calcium and ionised calcium concentrations may occur in peripancreatic fat saponification.[20]

Cholesterol disorders may be a cause or a consequence of AP,[20] while sodium and potassium levels are influenced by gastrointestinal loss, kidney injury and inflammation.[21,22]

Dogs with chronic kidney disease, diabetes mellitus, hypothyroidism, hypoadrenocorticism or hyperadrenocorticism and dogs with a final diagnosis of pancreatic neoplasia were excluded because all these dis- eases could be associated with AP and with abnormal SNAP® cPLTM test results. They could also influence the clinical signs, mortality rate and laboratory parameters considered in this study.

In the present study, alterations in serum creatinine and sodium con- centrations were identified as significant factors of poor outcome in dogs with pancreatitis. Hypothermia at the time of admission was not

associated with a negative outcome, which is not in agreement with a previous study.[2] The remaining parameters (respiratory rate, temperature, Hct, WBC, total protein, albumin, cholesterol, total calcium, calcium and potassium) did not correlate with a poor prognosis.

In our study, OR values of serum creatinine and sodium supported the positive association between azotaemia and negative outcome or hyponatraemia and negative outcome (Table 2).

Azotaemia has been reported as a prognostic marker in canine AP. Mansfield et al. found that dogs with a renal damage score of 2 (anuria or azotaemia > 1.5-fold increase in serum urea and creatinine concentrations) had a higher mortality rate than dogs with a renal damage score of 0 or 1. However, as the renal damage score was part of a multi-organ clinical severity index, azotaemia was not directly associated with prognosis.[8] In another study, azotaemia was present in 55% of dogs with AP, but was not considered to have prognostic significance.[2] Indeed, in human medicine, acute kidney injury (AKI) is a common complication of severe pancreatitis, which increases the risk of death.[23–25] AKI can be the result of hypoxaemia, oxidative stress, decrease in renal perfusion and hypovolaemia caused by AP.[25] The use of serum (symmetric dimethylarginine)[26] and urinary markers[27] (i.e. albumin, γ-glutamyl transferase) of AKI would have been helpful to identify patients with preclinical grades of AKI.

During AP, hyponatraemia can occur because of gastrointestinal loss, peritoneal effusion, kidney injury and systemic inflammatory response syndrome.[28,29]

In our study, 89.6% of dogs showed vomiting or diarrhoea, so gastrointestinal loss was the most probable cause of the hyponatraemia. Gut barrier damage could have played a prognostic role in these dogs, caused by possible bacterial translocation.[30]

Study limitations

There were a number of limitations to our study, including a lack of histopathology. It would also have been interesting to assess urinary output and natriuresis because serum sodium is influenced by renal excretion and anuric/oliguric patients have a worse outcome.[31] Although patients with endocrine disorders were excluded from the study, it is not possible to affirm that the dogs that died early did not have preclinical stages of endocrine disorders.

Finally, although all the dogs in the present study received similar medical management, the AP therapy included analgesia with opioid drugs, fluid therapy, antiemetic drugs, such as maropitant, and anta- cids, such as ranitidine or omeprazole. None received fresh frozen plasma infusion. We did not consider the effects of different drugs and dosages on mortality.

The present study examined prognostic parameters in canine AP that can be easily assessed in veterinary clinical practice. At the time of diagnosis, the assessment of serum sodium and serum creatinine concentrations may be helpful in evaluating the risk of death.

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