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Original article

A correlation between the Canine Inflammatory Bowel Disease Activity Index score and the histopathological evaluation of the small intestinal mucosa in canine inflammatory bowel disease

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Abstract

The aim of this study was to assess the degree of correlation between the intensity of clinical symptoms and the macroscopic and histopathological evaluation of the small intestinal mucous membrane in dogs. The results point to a statistically significant correlation between the values of the CIBDAI index and the histopathological assessment of the duodenum mucous membrane in patients with minor and moderate intensity of the disease. The lowest correlation coefficient was obtained for the indicator comparing macroscopic and histopathological evaluations. A positive correlation between the CIBDAI score and the histopathological index offers a base for applying it in the monitoring and treatment of mild, moderate and severe cases of canine inflammatory bowel disease.

Key words: inflammatory bowel disease (IBD), CIBDAI, histopathological index, dog

Introduction

Canine inflammatory bowel disease (IBD) is a diversified group of intestinal disorders characterized by cellular infiltration of the mucous membrane in the lamina propria area (Craven et al. 2004, Allenspach et al. 2006, Allenspach et al. 2007, Jergens and Simpson 2012). In gastroenterology centers, canine inflammatory bowel disease is diagnosed in view of the results of histopathological examinations of the intestinal mucous membrane and by ruling out other known

causes of enteritis based on hematological tests, biochemical blood tests, parasitological and microbiological examinations of feces and provocative food tests (Ridgway et al. 2001, Simpson and Jergens 2011). Analyses of clinical symptom intensity are an important part of the diagnostic procedure. From the clinical perspective, the discussed disease produces no specific symptoms. The most frequently observed symptoms are recurrent vomiting and diarrhea, observed in 70% to 90% of dogs, and the ineffectiveness of prior treatment. Unlike in humans, the inflammatory pro-

cess in dogs affects mostly the small intestine, especially the duodenum, and it is determined in more than 3/4 of IBD cases (Gaag and Happe 1990, Jacobs et al. 1990, Rudolf et al. 2005). In 2003, based on an analysis of the most frequent clinical symptoms, Jergens proposed a set of assessment criteria – the Canine Inflammatory Bowel Disease Activity Index – CIBDAI (Jergens et al. 2003). The main purpose of the CIBDAI index was to classify inflammation intensity, monitor treatment and detect early relapses. The available sources support the conclusion that the clinical image in the progression of canine inflammatory bowel disease is determined by the location of the inflammatory process and the intensity of histopathological lesions (German 2003, Munster et al. 2006, Garcia-Sancho et al. 2007). To date, the results of histopathological examinations of endoscopic specimens have been regarded as the decisive factor in the diagnostic process. In view of the scope of histopathological lesions, the patients are classified into groups with minor, moderate or severe progression of chronic enteritis (group classification determines prognosis and treatment). It may be expected that the suitability of the CIBDAI as a diagnostic tool is determined by the correlation between index values and the intensity of histopathological lesions. Patients with higher scores should be characterized by more advanced lesions in the intestinal mucous membrane. A positive correlation between the clinical index (CIBDAI) and the histopathological index will support a more accurate diagnosis of canine inflammatory bowel disease and effective treatment monitoring.

The aim of this study was to evaluate the correlation between the intensity of clinical symptoms and the macroscopic and histopathological assessment of the small intestinal mucous membrane.

Materials and Methods

The 55 animals selected for the experiment displayed symptoms characteristic of inflammatory bowel disease, including chronic diarrhea specific of the small intestine, and vomiting of varied intensity and frequency. The intensity of those symptoms was assessed based on the CIBDAI index proposed by Jergens (Table 1). Systemic diseases, infective and parasitic infestations, antibiotic responsive diarrhoea (ARD), food responsive diarrhoea (FRD), were excluded in all patients. Full clinical and laboratory examinations have been performed including blood hematology and biochemistry (also Spec cPL and TLI), fecal microbiological and parasitological examination and also imaging techniques (RTG and USG)

in every patient qualified for the study (Simpson and Jergens 2011). The animals were finally classified for the experiment based on the results of endoscopic and histopathological analyses of intestinal mucosa sections. For the comparative evaluation 20 patients have been randomly chosen showing a predominance of lymphocytic infiltration of the duodenum lamina propria. The dogs were divided into three groups according to the CIBDAI index score. The first group consisted of seven dogs with scores from 4 to 5 pointing to mild intensity of the disease. The second group consisted of seven animals with moderate intensity of clinical symptoms scoring from 6 to 8 points. The last group comprised six patients with total scores in excess of 9 points. The correlation coefficient between the clinical evaluation of symptom intensity (CIBDAI score), the macroscopic evaluation of the endoscopic image of the duodenal mucous membrane and the intensity of histopathological lesions, as well as the correlation index between macroscopic and histopathological evaluations of the mucous membrane were computed in each group of IBD patients.

The biochemical indicators were determined using the Idexx VetStat device. Blood samples were obtained from the anterobrachial vein in identical conditions. The final IBD diagnosis was formulated based on the results of endoscopic and histopathological examinations of the specimens collected.

Endoscopic examinations of the anterior section of the alimentary system were performed after a 24-hour fasting period, and no liquid was administered 6 hours before the examination. The ileum was examined during colonoscopy, the patients were fasted for 48 hours and received *per os* 0.9% NaCl at a dose 30 do 40 ml per kilogram of body weight 24 and 20 hours prior to colonoscopy. Furthermore, an enema of warm water should be performed 24 hours and 4 hours before the examination. The examination was conducted under complex anesthesia. The patients were premedicated with atropine at 0.05 mg/kg body weight and xylazine at 0.1 mg/kg body weight IM. Anesthesia was induced using ketamine at 5 mg/kg body weight IV according to the produced anesthetic effect. The mucous membrane of the pharynx was anesthetized with a 5% lignocaine solution. A spring-loaded gag was placed on the fangs. The examination was performed with the patient positioned on the left side. The endoscopic examination was carried out using the Olympus GIF 145 flexible videoendoscope with working length of 1030 mm and diameter 9.8 mm. In patients heavier than 30 kg, the CF-Q165L colonoscope with working length of 1680 and diameter of 12.8 mm was used. The intensity of macroscopic lesions was assessed on the following scale: 0 – no lesions, normal image; 1 – minor brittle-

Table 1. Criteria for the assessment of symptom intensity as proposed by Jergens (2003).

| | | |
|--------------------------------|---|---|
| I. Activity/emotional attitude | 0 | Appropriate |
| | 1 | somewhat decreased |
| | 2 | moderately decreased |
| | 3 | significantly decreased |
| II. Appetite | 0 | Normal |
| | 1 | somewhat decreased |
| | 2 | moderately decreased |
| | 3 | significantly decreased |
| III. Vomiting | 0 | none |
| | 1 | mild (1 episode/week) |
| | 2 | moderate (2-3 episodes/week) |
| | 3 | severe (>3 episodes/week) |
| IV. Feces consistency | 0 | Appropriate |
| | 1 | somewhat loose, presence of blood and/or mucus in feces |
| | 2 | visibly loose with or without blood and/or mucus in feces |
| | 3 | watery diarrhea |
| V. Defecation frequency | 0 | Appropriate |
| | 1 | somewhat increased (2-3 times a day) |
| | 2 | moderately increased (4-5 times a day) |
| | 3 | significantly increased (>5 times a day) |
| VI. Bodyweight loss | 0 | None |
| | 1 | minor (<5% loss) |
| | 2 | moderate (5-10% loss) |
| | 3 | significant (>10% loss) |

Table 2. Criteria for a histopathological evaluation of the mucous membrane.

| I – Epithelium | Classification of lesions |
|---|--|
| Size of erythrocytes | no lesions (0) to significantly changed (3) |
| Continuity of structure | no damage (0) to significant damage (3) |
| Number and size of goblet cells/100 enterocytes | normal (0) to significantly changed, large quantity of mucus (3) |
| Cellular infiltration | none (0) to significant infiltration (3) |
| II – Lamina propria | |
| Cellular infiltration | none (0) to significant infiltration (3) |
| Fibrosis | none (0) to significant fibrosis (3) |
| Lymphectasia | none (0) to significant lymphectasia (3) |
| III – Crypts | atrophy |
| None (0) to significant atrophy (3) | |
| Hypertrophy – shape change | none (0) to significant hypertrophy (3) |
| Proliferation – hyperplasia | none (0) to significant proliferation (3) |
| Diversification of goblet cells | none (0) to significant diversification (3) |
| Presence of inflammatory cells | none (0) to significant infiltration (3) |
| IV – Villi | |
| Structure (length, width, shape) | normal (0) to significant change in structure (3) |

ness of the mucous membrane, reddening; 2 – mucous membrane is somewhat plicated, lusterless, with pseudo-dyfteroidal surface deposits; 3 – mucous membrane resembles “paving blocks”, showing erosions and significant brittleness.

Six mucous membrane specimens from the duodenum, jejunum and ileum were collected from all patients for histopathological evaluation using biopsy forceps FB-24K-1-Olympus or or FB-24U-1-Olympus. The mucous membrane specimens were placed

in neutralized 10% formalin with pH 7.4 and embedded in paraffin blocks. The obtained microtome sections were stained with hematoxylin and eosin (HE). The stained histological specimens were viewed under a microscope at different magnifications to determine the type and degree of morphological damage. Image analyzing software (LUCIA 3.52a, PANASONIC digital camera, light microscope B1) was applied to determine the percentage share of cells in the lamina propria and the presence of intraepithelial lymphocytes in the collected villi.

The histopathological examination, according to the directives published in Day's and Washabau's articles, evaluated not only the cellular infiltration but also the degree of mucosal structural damage (Table 2; Day et al. 2008, Washabau et al. 2010). If the examination revealed a minor increase in the cellular infiltration of the lamina propria and the predominance of minor morphological damages to the mucous membrane, the degree of histopathological lesion was graded as minor and given the score of 1. Increased cellular infiltrations and more extensive morphological damages to the mucous membrane were graded as moderate and given the score of 2, and significantly higher cellular infiltrations in the lamina propria with major damage to the mucous membrane, significant fibrosis and numerous erosions in the intestinal epithelium were evaluated as advanced and identified by a score of 3. The authors are aware of the limitations of such evaluation, which is subjective, but biopsy specimens were analyzed by a histopathologist experienced in intestinal biopsy assessment (Willard et al. 2008, Washabau et al. 2010, Simpson and Jergens 2011).

The correlations between the above indicators were tested by means of the Spearman's rank correlation coefficient. A positive value of the rank correlation coefficient was assumed. The tested hypothesis was $H_0: r_s = 0$ with alternative hypothesis $H_1: r_s > 0$ (right-sided critical area) at the significance level of $p = 0.05$. The critical values were read from Olds tables where the critical value for $n = 6$ is 0.8285 and for $n = 7$ – 0.7142 (Ramsey 1989).

The study obtained the approval of the local research ethics committee.

Results

In the first group with mild clinical disease symptoms, four dogs were given a CIBDAI score of 4 and three dogs – of 5. Vomiting was observed in 6 dogs, while 5 animals were affected by small intestinal diarrhea. In the second group, five dogs scored 7 points and two dogs – 8 points. Vomiting was observed in all

patients of the second group, 5 animals suffered from diarrhea, and three dogs showed a significant decrease in appetite. In the group of patients showing acute symptoms of the disease, five patients scored 9 points and one patient – 11 points on the CIBDAI scale. All dogs in that group suffered from vomiting, diarrhea, loss of appetite, body weight loss and deterioration of coat quality (lusterless, poorly set and breaking).

Results of macroscopic examinations of the duodenal mucous membrane

Group I

In the group of patients with mild clinical symptoms, a normal macroscopic image of the mucous membrane was found in one patient, and minor reddening of the mucous membrane with slight local surface plication was observed in five patients who received 1 point each for minor lesions. In one patient, the lesions were more advanced, and they were classified as moderate with 2 points (Table 3).

Table 3. CIBDAI scores and the results of macroscopic and histopathological evaluations of the duodenal mucous membrane in dogs with mild, moderate and advanced symptoms of IBD.

| Group | Dog | CIBDAI score | Macroscopic score of duodenum | Histopathological score of duodenum |
|-------|-----|--------------|-------------------------------|-------------------------------------|
| I | A | 4 | 0 | 1 |
| | B | 5 | 1 | 2 |
| | C | 4 | 1 | 1 |
| | D | 4 | 1 | 1 |
| | E | 5 | 1 | 1 |
| | F | 4 | 1 | 1 |
| | G | 5 | 2 | 2 |
| II | A | 7 | 2 | 2 |
| | B | 8 | 2 | 2 |
| | C | 8 | 2 | 2 |
| | D | 7 | 1 | 1 |
| | E | 7 | 2 | 2 |
| | F | 7 | 2 | 2 |
| | G | 7 | 1 | 2 |
| III | A | 9 | 3 | 2 |
| | B | 9 | 2 | 2 |
| | C | 9 | 3 | 3 |
| | D | 9 | 3 | 3 |
| | E | 11 | 3 | 3 |
| | F | 9 | 3 | 3 |

Group II

In five dogs, the intensity of macroscopic lesions was evaluated as moderate – 2 points. The surface of the mucous membrane was clearly plicated and reddened. Evident brittleness of the mucous membrane and minor bleeding were observed during the collec-

tion of biopsy specimens and endoscope movement. The macroscopic images of the remaining two patients were given a score of 1 point (Table 3).

Group III

In this group of patients, the surface of the duodenal mucous membrane was brittle, evidently uneven with a “paving blocks” type of texture covering a large area; erosion and numerous pseudo-dyfteroidal deposits were visible. The above macroscopic lesions were observed in three patients and they were classified as significant – 3 points. In one dog, the intensity of macroscopic lesions was classified as moderate, scoring 2 points (Table 3).

Results of histopathological examinations of specimens from the duodenal mucous membrane

Group I

The results of histopathological examinations in the group of patients showing mild disease symptoms were diversified. In five dogs, minor deformation of the villi and minor damage to the epithelium were observed. The epithelium was even, while a low epithelium with signs of atrophy was reported locally in dogs A, C and D. A small number of goblet cells and mild lymphectasia accompanied a slight increase in the number of cells in the lamina propria. The number of crypts was normal. Some villi showed signs of hyperemia. In this group of patients, an average of 62% plasmocytary cells and 37% lymphocytary cells were observed in the lamina propria. The number of intraepithelial lymphocytes did not exceed 4 lymphocytes per 100 enterocytes. The above lesions were classified as minor and given a score of 1 point. In two dogs (B and G), the lesions found were more advanced than in six other members of the group with moderate symptoms of the disease (CIBDAI scores 6-8). The percentage composition of cells in the lamina propria also differed from that determined in patients with CIBDAI scores of 4 to 5, and it contained 40% eosinophilic cells, 43% lymphocytes and 17% plasmocytary cells (Table 3).

Group II

Deformed villi and moderate damage to the epithelium were observed in six patients. The epithelium was plicated, locally low, with atrophic changes. The histopathological image revealed a small number of goblet cells, lymphectasia, a large number of lamina propria cells and small numbers of fibrocytes and fibroblasts. The number of crypts was normal, but the number of inflammatory cells was significantly increased. Signs of hyperemia were visible in some villi. The lamina propria comprised 38% plasmocytary

cells, 41% lymphocytary cells and 21% eosinophilic cells. The number of intraepithelial lymphocytes did not exceed 4 per 100 enterocytes. The described histopathological lesions can be classified as moderate on the Sydney scale, scoring 2 points. In one dog, less intensive histopathological lesions were found with 40% infiltration by lymphocytes and 17% by plasmocytary cells, scoring 1 point (Table 3).

Group III

In group III, the following lesions were observed: intestinal villi of diversified size, low epithelium, a moderate number of erosions in the epithelial continuity (3-5 per group of several villi), visible mucus bands on villi surface, highly numerous cells in the lamina propria and a small number of goblet cells, a high number of fibrocytes and fibroblasts. In most visible crypts, changes in shape and moderate lymphectasia were observed. Significant fibrosis of the villi was also found. There lamina propria had the following composition: 34% plasmatic cells, 39% lymphocytes and 27% eosinophilic cells. The number of intraepithelial lymphocytes was low, not exceeding 2. The above lesions were detected in four dogs and classified as “advanced”, scoring 3 points. In two patients (A, B), the intensity of histopathological lesions was similar to that found in most group II dogs, classified as moderate and scoring 2 points (Table 3).

Discussion

An analysis of the intensity of clinical symptoms is an important stage of the diagnostic process dealing with inflammatory bowel disease. Due to an absence of specific symptoms, various authors have evaluated the intensity of the disease based on different clinical symptoms. Based on an analysis of the most frequent clinical symptoms, Jergens (2003) proposed a set of assessment criteria, termed as the Canine Inflammatory Bowel Disease Activity Index – CIBDAI. As a tool enabling the initial classification and comparison of disease intensity among various patients, the CIBDAI also supports the selection of the most appropriate treatment method, an evaluation of its effectiveness and the early detection of possible relapses (Jergens 2004). For the discussed index to demonstrate the required degree of clinical effectiveness, an appropriate level of correlation with the histopathological index is required. Histopathological examinations of endoscopic specimens of intestinal tissue are regarded as the gold standard (Jenkins et al. 1997, Willard et al. 2008). A correct diagnosis requires 5 to 7 biopsies of each intestinal segment, lesion analyses in every mucous membrane component and

a determination of the number of cells in the lamina propria area (Day et al. 2008). A positive correlation between the CIBDAI and the results of a histopathological examination supports diagnosis and treatment, nevertheless, the final diagnosis would be formulated based on the results of a histopathological examination. The presence of correlations between the CIBDAI and the histopathological index facilitates treatment because a decrease in the intensity of symptoms during therapy suggests an improvement in the histopathological structure of the mucous membrane. It should be noted, however, that the existence of such a correlation during the progression of the disease is not indicative of its presence following IBD treatment.

Jergens et al. (2003) confirmed the positive correlation between the above indicators without differentiating between the different levels of symptom intensity. In most cases, the more advanced the lesions, the higher the correlation between symptom intensity and the values of biochemical indicators and histopathological changes. The results of this experiment point to a correlation between CIBDAI scores and the intensity of histopathological lesions in patients showing mild (group I) and moderate (group II) symptoms of the disease. In both groups, correlation coefficients exceeded critical values, suggesting the presence of a correlation between the discussed indicators. The correlation coefficient in group II yielded higher values, pointing to a higher correlation between CIBDAI scores and the intensity of histopathological changes in patients displaying moderate symptoms of the disease. In the group of patients

showing the most intense clinical symptoms, the correlation coefficient approximated the critical value (0.8285), and the difference resulted from a lower number of patients in the studied group (Table 4).

A positive correlation between the intensity of clinical symptoms and histopathological lesions in groups I and II is of special importance because the majority of patients showed mild or moderate clinical symptoms. Similar results were reported by Jergens who also validated the positive correlation between the CIBDAI score and histopathological changes in IBD (Jergens 2003). A satisfactory correlation between clinical indicators and histopathological evaluation results has not been found by all authors. Allenspach et al. (2007) did not validate the correlation between CIBDAI scores and the results of histopathological and macroscopic examinations of the mucous membrane. In the above study, the correlations between the discussed indicators were compared in chronic enteropathies, including food allergy and protein-losing enteropathy, which could have significantly influenced the value of the coefficients analyzed. McCann did not observe correlations between histopathological lesions and the CIBDAI score, the levels of C-reactive protein and micro-albumins in urine (McCann et al. 2007). In the above study, the absence of correlations could have resulted from the fact that only 16 dogs participated in the experiment. None of the cited authors classified patients into groups characterized by various disease intensity. A histopathological examination is a subjective evaluation, and this fact could explain extensive variations in the results reported. Histopathological evaluations are largely determined by the specimen collection method, the number of samples, the sampled location and, above all, the histopathologist's experience. For this reasons, analyses of the biopsy specimens must be performed by skilled personnel specializing in IBD (Day et al. 2008, Willard et al. 2008, Simpson and Jergens 2011).

The present study revealed insignificant correlations between the results of macroscopic and histopathological evaluations in patients with inflammatory bowel disease. The value of the correlation coefficient was much below the critical value in all three experimental groups, and it was even lower than the coefficient comparing CIBDAI with macroscopic evaluation results. The above suggests that macroscopic evaluations of the small intestinal mucous membrane does not provide a sufficient basis for the formulation of a diagnosis. Minor changes in mucous membrane morphology can be accompanied by highly advanced histopathological lesions, and the reverse applies. Similar results were reported by a wide spectrum of authors (German et al. 2003, Fefferman and

Table 4. Spearman's rank correlation coefficients for the analyzed indicators in dogs with different intensity of IBD symptoms.

| Group | CIBDAI-macro | CIBDAI-histopathological | Macro-histopathological |
|-------|--------------|--------------------------|-------------------------|
| I | 0.678571 | 0.741071* | 0.375000 |
| II | 0.625000 | 0.812500* | 0.525000 |
| III | 0.657143 | 0.815714 | 0.514286 |

Note:

* correlation coefficient above critical value, i.e. a correlation exists between those indicators (right-sided critical area) at the significance level of $p=0.05$

CIBDAI-macro – a comparison of the CIBDAI score and the macroscopic evaluation of the small intestinal mucous membrane

CIBDAI-histopathological – a comparison of the CIBDAI score and the histopathological evaluation of the small intestinal mucous membrane

Macro-histopathological – a comparison of the macroscopic evaluation score and the histopathological evaluation score for the small intestinal mucous membrane

Farrel 2005, Garcia-Sancho et al. 2007, Willard et al. 2008), and as the result, the WSAVA recommended a higher number of biopsies from individual segments of the alimentary system regardless of the observed macroscopic image of the gastric and intestinal mucosa (Day et al. 2008). In this study no correlation between the macroscopic evaluation of the duodenum and the clinical activity index was observed in any group. The above mentioned indicates, that the degree of disease intensity cannot be estimated based on the macroscopic appearance of the intestinal mucosa. Similar results acquired Allenspach and Garcia-Sancho (Allenspach et al 2007, Garcia-Sancho 2007).

A correlation between the CIBDAI score and the histopathological evaluation of the duodenum mucous membrane was determined in patients showing mild and moderate symptoms of IBD. A similar correlation coefficient would have been obtained in group III, but critical values could not be exceeded due to a lower number of patients. A comparison of the macroscopic evaluation index and the histopathological index yielded the lowest values of the correlation coefficient. A positive correlation between the CIBDAI score and the histopathological index renders it suitable for monitoring and treating canine inflammatory bowel disease, provided that the said correlation is validated for the administered drug.

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