A RETROSPECTIVE STUDY ON 120 NATURAL CASES OF CANINE EHRLICHIOSIS

J. VAN HEERDEN*

ABSTRACT: Van Heerden J. A retrospective study on 120 natural cases of canine ehrlichiosis. Journal of the South African Veterinary Association (1982) 53 No. 1 17-22 (En) Department of Medicine, Faculty of Veterinary Science, University of Pretoria, Box 12580, 0110 Onderstepoort, Republic of South Africa.

In a retrospective study on 120 natural cases of canine ehrlichiosis, it was found that cases were presented in all months of the year. The disease was diagnosed in 26 different breeds amongst which the German Shepherd was the best represented. Of the different breeds of dog, German Shepherds showed the highest incidence of chronic cases as well as the highest mortality rate. In a randomly selected sample of 50 dogs, the clinical signs of canine ehrlichiosis were found to be mainly non-specific. The terms acute, subacute and chronic are proposed to describe the different stages of disease. The total white cell count was found to be of prognostic value. Treatment with either doxycycline or oxytetracycline was found to be effective in most of the cases. Blood transfusion was the most important method of supportive therapy.

INTRODUCTION

Canine ehrlichiosis has been described in many different breeds of dogs1 2 11 17 as well as in many different parts of the world1. The relatively great susceptibility of the German Shepherd Dog has been suggested by the studies of Spence, Giam & Theis11; Huxsoll et al.4 and Kloper & Nobel8.

The different stages of the disease as well as the clinical signs thereof have been described by Walker et al.8 and Buhles, Huxsoll & Ristic7. Troy et al.12 also reported on the relative incidence of the various clinical signs in a series of natural cases.

This report is a retrospective study of natural cases of canine ehrlichiosis.

MATERIALS AND METHODS

Data was collected from 120 clinical cases of ehrlichiosis presented for diagnosis and treatment over a 3-year period to the Department of Medicine, Faculty of Veterinary Science, University of Pretoria. The majority of cases (108) originated from the Pretoria District which includes the city and adjacent rural areas. Most cases came from the northern suburbs and adjacent areas. Only 12 cases came from elsewhere in Southern Africa namely:

(a) a Bull-Mastiff and a Pomeranian from Rustenburg, Transvaal
(b) a Beagle from Jan Kempdorp, Northern Cape
(c) a Samoyed from Johannesburg, Transvaal
(d) 8 German Shepherd Dogs from military operational areas which include areas in South West Africa/ Namibia.

On admittance the date, breed, age, sex and body mass were recorded. All cases were also subjected to a full physical examination, examination of a peripheral capillary blood smear and a haematological investigation of venous blood; in some cases serum was collected for the determination of serum proteins and an electrophoretic study.

The diagnosis of ehrlichiosis in all cases (except in dogs with severe pancytopenia) was confirmed by the demonstration of morulae of E. canis in peripheral blood smears stained with Diff-Quik (Harleco).

The diagnosis of ehrlichiosis in dogs with severe pancytopenia was based on:

1. (1) clinical signs of disease
2. (2) the presence of a leucopenia, an anaemia and a thrombocytopenaia
3. (3) the presence of a hypergammaglobulinaemia
4. (4) post-mortem findings (of which a variable plasma-cell infiltration into many organs and tissues was the most outstanding histopathological finding).

Clinical cases of ehrlichiosis were classified as either acute/subacute or chronic. A case was classified as chronic based on the presence of

(a) clinical signs of chronic disease such as chronic progressive loss in body mass, chronic intermittent pyrexia, epistaxis, etc.
(b) a white cell count of 6 × 10⁹/lt or less, and
(c) the presence of a hypergammaglobulinaemia.

All other cases were classified as acute/subacute.

The incidence of the various clinical signs amongst such randomly-selected cases was expressed as a percentage thereof. These cases were divided into 5 groups according to their respective total white cell counts. The percentage mortality in each group was established. They were also subdivided into 4 groups according to their respective red cell counts and again the percentage mortality in each group was established.

Cases were treated as follows:

Specific treatment with one of the following drugs was given:

(i) Oxytetracycline (Terramycin capsules, Pfizer) orally at a dosage rate of 100 mg/kg once daily or 50 mg/kg twice daily for not less than 10 days.
(ii) Oxytetracycline (Liquamycyn – Pfizer) intravenously at a dosage rate of 5-10 mg/kg once daily for not less than 6 days. If the drug was given for less than 6 days, it was followed by the oral administration of oxytetracycline as indicated above until the dog was treated for not less than 10 days in total.
(iii) Doxycycline (Doxyvet, Milvet) either orally or intravenously at a dosage rate of 5-10 mg/kg for not less than 10 days.

Supportive treatment which was given in some instances, consisted of one or more of the following:

(i) A blood transfusion. A transfusion with fresh
blood was given whenever an anaemic dog was presented in a bleeding state. (Fresh blood being blood collected immediately prior to transfusion.) Anaemic, non-bleeding dogs were given stored blood. Depending on the physical state of the patient, a blood transfusion was usually given when the haematocrit dropped to below 0,20. A dosage of 40 ml blood/kg was usually aimed for.

(ii) Intravenous fluids (Sodium Chloride 0,45 % m/v and Dextrose 2,5 % m/v injection or polyionic Plasmalyte B, Sabax, Aerotan, Johannesburg).

(iii) Essential phospholipids at a dosage rate of one tablet (Essentiale, Nattermann) twice daily.

Concurrent infection with B. canis was treated with one or more of the following:

(i) Diminazine (Berenil, Hoechst) at a dosage rate of 3,5 mg/kg intramuscularly.

(ii) Trypan blue (Trypan Blue, Centaur Labs) at an approximate dosage rate of 10 mg/kg intravenously.

(iii) Imidocarb dipropionate (Forray-65, Coopers) at a dosage rate of 6 mg/kg subcutaneously.

(iv) Phenamidine isethionate 5 % (Phenamidine, Maybaker) at a dosage rate of 0,4 ml/kg subcutaneously.

In severe chronic cases one or more of the following drugs were used:

(i) Prednisolone (Medrol 4 mg tabs, Upjohn) at an oral dosage rate varying from 0,5-2 mg/kg daily up to 28 days.

(ii) Nandrolone (Laurabolin 50 mg/ml, Intervet) at an intramuscular daily dosage rate of 150 mg up to 19 days.

(iii) Levamisole (Tramisol 2,5 % m/v I.C.I.) at an oral daily dosage rate of varying from 3,3-10,0 mg/kg for up to 70 days.

RESULTS

Average monthly presentation of cases

The monthly distribution of 120 cases of canine ehrlichiosis over a 3-year period is given in Fig. 1.

Clinical cases occurred in all months of the year. The highest number of cases were seen during the months April (16), May (16) and June (17). The majority of cases were presented during the first 6 months of the year.

Breed frequency

The 120 clinical cases of ehrlichiosis included dogs of 27 different breeds and crossbreds:

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>German Shepherd Dogs and German Shepherd Dog crosses</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Doberman Pinchers</td>
<td>17</td>
</tr>
<tr>
<td>Crossbreds</td>
<td>14</td>
</tr>
<tr>
<td>Labradors (and Labrador-crosses)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Bull Terriers</td>
<td>6</td>
</tr>
<tr>
<td>Fox Terrier Crosses</td>
<td>6</td>
</tr>
<tr>
<td>Boerboel</td>
<td>4</td>
</tr>
<tr>
<td>Collie</td>
<td>3</td>
</tr>
<tr>
<td>Pomeranian</td>
<td>3</td>
</tr>
<tr>
<td>Rottweiler</td>
<td>3</td>
</tr>
<tr>
<td>St Bernard</td>
<td>3</td>
</tr>
<tr>
<td>Pyrenian Mountain Dog</td>
<td>3</td>
</tr>
<tr>
<td>Greyhound</td>
<td>3</td>
</tr>
<tr>
<td>Other: (Boxer, Bull Mastiff, Bassett, Beagle, Dalmation, Irish Setter, Great Dane, Keeshond, Maltese Poodle, Old English Sheepdog, Schipperke, Samoyed, Scottish Terrier, Rhodesian Ridgeback, Wirehaired Terrier)</td>
<td>18</td>
</tr>
</tbody>
</table>

The 3 best represented groups/breeds were:

(a) German Shepherd Dogs and German Shepherd Dog crosses

(b) Doberman Pinchers

(c) Crossbreds

Chronic cases within the different breeds

Chronic cases of ehrlichiosis occurred in 16 different breeds;

<table>
<thead>
<tr>
<th>Breed</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>German Shepherd Dog</td>
<td>14</td>
</tr>
<tr>
<td>Labrador</td>
<td>5</td>
</tr>
<tr>
<td>Crossbreds</td>
<td>4</td>
</tr>
<tr>
<td>Bull Terrier</td>
<td>3</td>
</tr>
<tr>
<td>Collie</td>
<td>2</td>
</tr>
<tr>
<td>Bull Mastiff</td>
<td>2</td>
</tr>
<tr>
<td>Pomeranian</td>
<td>2</td>
</tr>
<tr>
<td>Boerboel</td>
<td>1</td>
</tr>
<tr>
<td>Wirehair Terrier</td>
<td>1</td>
</tr>
<tr>
<td>Dobermann</td>
<td>1</td>
</tr>
<tr>
<td>Greyhound</td>
<td>1</td>
</tr>
<tr>
<td>Fox Terrier</td>
<td>1</td>
</tr>
<tr>
<td>St Bernard</td>
<td>1</td>
</tr>
<tr>
<td>Rhodesian Ridgeback</td>
<td>1</td>
</tr>
<tr>
<td>Keeshond</td>
<td>1</td>
</tr>
<tr>
<td>Pyrenian Mountain Dog</td>
<td>1</td>
</tr>
</tbody>
</table>

Forty-one or 34,2 % of the 120 cases were classified as chronic cases. Fourteen or 58,3 % of the German Shepherd Dog cases were classified as chronic cases.

Incidence of mortality

Thirty or 25 % of the 120 cases died. Mortality occurred in 13 different breeds:
Incidence of clinical signs
The incidence of specific clinical signs amongst the randomly-selected cases was as follows:

- Anorexia: 84%
- General depression: 84%
- Anaemia: 76%
- Fever: 70%
- Peripheral lymph node enlargement: 64%
- Loss in body mass: 59%
- Splenomegaly: 36%
- Epistaxis: 22%
- Mucopurulent ocular and/or nasal discharges/conjunctivitis: 8%
- Icterus: 4%
- Vomition: 4%
- Limb-oedema: 2%
- Bronchial râles: 2%

"Anorexia"—a varying degree of anorexia was reported by owners and observed amongst hospitalized cases. In most cases only a reduced appetite or an intermittent anorexia was observed. Total anorexia was only recorded from dogs in the acute (febrile stage) or terminal chronic phase of the disease.

"General depression"—a varying degree of general depression was observed and dogs often showed only intermittent listlessness.

"Anaemia"—the clinical diagnosis of anaemia corresponded well with the laboratory diagnosis. According to the latter, 84% of the cases were anaemic and on physical examination 75% of the cases were found to be anaemic.

"Loss in body mass"—this varied from a very slight drop in condition to extreme emaciation in advanced chronic cases.

"Other haemorrhages"—these included haemorrhages in the skin and into the chambers of the eye.

Incidence of blood parasites other than Ehrlichia canis
A concurrent infection with Babesia canis was found in 20 of the 50 randomly-selected dogs. Gametocytes of Hepatozoon canis were also found in peripheral blood smears in 8 of the cases.

The relationship between leukopaenia and mortality
The total white cell counts of 50 cases are given in Table 1.

More than 41% of the German Shepherd Dogs did not survive the disease.

Table 1: CLASSIFICATION OF EHRlichia CASES ACCORDING TO THEIR TOTAL WHITE CELL COUNTS

<table>
<thead>
<tr>
<th>Group</th>
<th>White cell count ( \times 10^9/l )</th>
<th>Number of cases</th>
<th>% Mortality in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0-1</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>B</td>
<td>1-1-2</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>C</td>
<td>2-1-6</td>
<td>11</td>
<td>9,1</td>
</tr>
<tr>
<td>D</td>
<td>6-1-12</td>
<td>21</td>
<td>9,5</td>
</tr>
<tr>
<td>E</td>
<td>12+</td>
<td>9</td>
<td>22,2</td>
</tr>
</tbody>
</table>

The percentage mortality for the different groups A, B, C, D & E was 75, 100, 9,1, 9,5 and 22,5% respectively. All cases, except one, with a total white cell count of 2 \( \times 10^9/l \) or lower, died.

Relationship between red cell count and mortality
The results of classification of 50 clinical cases of ehrlichiosis according to their red cell counts are given in Table 2.

Table 2: CLASSIFICATION OF CLINICAL CASES OF EHRLICHIOSIS ACCORDING TO THEIR RED CELL COUNTS

<table>
<thead>
<tr>
<th>Group</th>
<th>Red cell count ( \times 10^9/l )</th>
<th>Number of cases</th>
<th>% Mortality within group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0-2</td>
<td>8</td>
<td>62,5</td>
</tr>
<tr>
<td>B</td>
<td>2-1-3</td>
<td>19</td>
<td>31,5</td>
</tr>
<tr>
<td>C</td>
<td>3-1-4</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>D</td>
<td>4+</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

There was a tendency towards greater mortality in more anaemic dogs.

Treatment
Thirty or 25% of the 120 cases did not survive the disease despite treatment (Fig 1). Most cases that died were either patients with severe pancytopaenia or cases complicated by concurrent infections with B. canis and/or H. canis.

Treatment of cases with severe pancytopaenia often was an expensive and prolonged commitment. The use of corticosteroids and/or anabolic steroids in a few cases did not seem to alter the outcome of severely pancytopaenic cases.

Two severely pancytopaenic cases were treated with laevamisole (antibiotic treatment was given at the same time) over an extended period of time (Table 3). One of them, Case A, was treated for 70 days at a daily oral dosage rate of 3,3 mg/kg and is one of 2 cases that recovered from severe pancytopaenia. The other patient, Case B, initially showed a good response to treatment, but subsequently deteriorated and died. There is, however, some uncertainty as to whether the owner continued with the treatment at home.

DISCUSSION

Average monthly distribution of cases
The highest number of clinical cases were presented during late autumn and early winter. With the exception of the month December, the lowest number of cases were presented during July, August, September and October. Cases of canine ehrlichiosis were, however, presented in all months of the year.

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If the relatively long (subclinical) subacute phase of the disease is kept in mind, then the observed monthly distribution of presented cases bears some resemblance to the monthly fluctuation in population size of *Rhipicephalus sanguineus* as found by Horak. (Horak IG, Department of Parasitology, Faculty of Veterinary Science, University of Pretoria, personal communication 1980). Horak found population numbers of *R. sanguineus* to be at its lowest during June, July and August with an increase in population size from September onwards. The population size started to decrease during April/May. More extensive studies on both population dynamics of *R. sanguineus* as well as on the incidence of canine ehrlichiosis in a dog population within the same area might well reveal a closer relationship.

It should also be borne in mind that the relatively long and variable duration of the subacute and chronic phases of the disease would make it very difficult to correlate presented clinical cases with seasonal fluctuation in tick numbers. Owners are often inclined to present dogs only when they show clear signs of disease - at which time the dog might well already be in the chronic stage of disease. It is impossible to determine the exact duration of the disease in a dog, even with the aid of haematological and serological parameters.

The small number of cases presented during December is probably misleading due to the fact that referrals to the Medicine Department during this period are usually very low. The drop in clinical cases during winter might well be ascribed to lower number of ticks.

### Breed-frequency

Although the presented figures do not represent the relative susceptibility of the different breeds in the dog population of the study area, they do seem to indicate an over-representation of the German Shepherd Dog. The breed frequency in the dog population within the study area has, however, not been determined. In a survey conducted by Osterhoff among 600 dog owners in the Pretoria-Johannesburg area and elsewhere in the Republic of South Africa, German Shepherd Dogs represented 5.3% of the dog population. Twenty-eight percent of the dogs in Osterhoff’s study were crossbreds and might well explain the relatively higher number of crossbreds suffering from ehrlichiosis in this study.

### Chronic cases/mortality within the different breeds

The fact that the percentage of chronic cases and the percentage mortality for German Shepherd Dogs was considerably higher than the same figures for all of the remaining dogs combined, might well be an indication of the relatively greater susceptibility of the German Shepherd Dog for *E. canis*. It might well be an indication of a decreased ability by this breed to develop a cell-mediated immunity against *E. canis*.

### Incidence of clinical signs

The clinical signs of canine ehrlichiosis are mainly nonspecific signs. This is indicated by the high incidence of clinical signs such as anorexia, general depression and anaemia. The recorded clinical signs in general agree with clinical features as described by Walker et al. and Buhles et al.

In an analysis of clinical signs in 30 cases of canine ehrlichiosis, Troy et al. recorded anaemia, loss in body mass, anorexia, general depression and a fever reaction as the most common clinical signs of ehrlichiosis.

The higher incidence of a fever reaction in this study is probably misleading. Factors such as transport of the dog to the clinic, a period of waiting in the waiting room and physical examinations at the outpatient clinic might have contributed to the observed fever-reaction. This is supported by the fact that patients often had normal rectal temperatures within 24 h of admittance and before treatment was initiated.

The relatively low incidence of epistaxis in the present investigation illustrates the fact that epistaxis should not be regarded as a classical clinical sign of canine ehrlichiosis.

Walker et al. described the course of clinical disease in canine ehrlichiosis as a fever phase followed by a subclinical phase which might proceed to a terminal phase. Buhles et al. described the subclinical phase as a mild chronic pancytopaenic phase and the terminal phase was described as a severe chronic pancytopaenic phase.

The terms acute, subacute and chronic should, however, be used to describe the different stages of canine ehrlichiosis. The term “subclinical” should not be used...
to describe the stage of disease following on the acute stage of disease, because “subclinical” implies the complete absence of clinical signs of disease. In my opinion this is not the case. Although dogs might only display subtle signs of disease, they are nevertheless present. These signs include one or more of the following: (intermittent) slight depression; varying degree of anorexia, often intermittent; varying degree of loss in body mass; mild enlargement of peripheral lymph nodes; mild anaemia. Describing the subacute phase as a mild chronic pancytopenic phase is also incorrect in that dogs in this stage often do not suffer from a pancytopenia. It should be stressed that it is often very difficult to distinguish between the different stages of canine ehrlichiosis.

Blood-parasites other than E. canis

The relatively common occurrence of a combined infection of B. canis and E. canis in the dog necessitates meticulous examination of peripheral blood smears, especially in so-called cases of biliary relapse.

Leukopaenia

A very high mortality rate occurred amongst dogs with a total white cell count of $2 \times 10^{12}/L$ and lower.

Although pancytopenia occurs in both the acute and chronic stages of the disease, the leukopaenia in the acute stage of the disease is usually less severe and of a relatively transient nature. Observations on the total white cell count of experimentally infected dogs in the acute stage of canine ehrlichiosis has shown it to be a less constant feature than anaemia and thrombocytopenia. The drop in total white cell count during acute stages was also less severe than in the chronic stages of the disease (author's unpublished data). Seamer & Snape also reported the changes in white blood cell counts to be the least striking of the haematological changes in the acute stage of the disease. Reardon & Pierce also reported a slight decrease in total leukocyte counts 14 days after infection.

In view of the high mortality rate found amongst severely leukopaenic dogs, the total white cell count thus seems to be of prognostic value in canine ehrlichiosis. A prognostic parameter is of great importance especially in chronic cases where treatment is often prolonged, expensive and unrewarding.

In the present investigation the mortality rate, based on red cell counts, was the highest amongst dogs with a red cell count of lower than $2 \times 10^{12}/L$. There was, however, not such a dramatic difference in mortality (as was the case in the white cell count groups) between the different groups of anaemic dogs.

Treatment

The high oral dosage rates of oxytetracycline have been used according to the recommendations of Immelman who has shown that such a dose rate would result in adequate blood levels of oxytetracycline for 24 h.

One of the most important supportive treatments in patients with canine ehrlichiosis is the administration of blood. In bleeding (thrombocytopenic) anaemic patients, a fresh blood transfusion should be given, whilst in non-bleeding anaemic patients one need not necessarily administer fresh blood. (Fresh blood here refers to blood that was collected immediately prior to transfusion.)

The decision to treat severely pancytopenic dogs with levamisole was based on:

1. Possible immunosuppression of the cell-mediated immune response in severe canine ehrlichiosis;
2. Observation that both monocyte-derived macrophages and antibodies are necessary to destroy or suppress the growth of E. canis in vitro;
3. The immuno-stimulant properties of levamisole.

Levamisole restores polymorphonuclear, macrophage or T cell functions such as random migration, phagocytosis and cell mediated cytotoxicity. Its effects are especially marked on hypofunctional cells. The effects of levamisole on leucocytes are brought about by its ability to increase intracellular levels of cyclic guanosine monophosphate and by reversing the inhibitory effects of cycle adenosine monophosphate (cAMP) elevating agents. On the contrary, levamisole also induces T cell differentiation, an apparently cAMP mediated phenomenon. A similar dual mechanism has also been suggested for thymic hormone. Like levamisole, thymic hormone specifically effect T cells and not B cells.

It is interesting to note that thymic atrophy has been a remarkable post mortem finding in experimentally induced canine ehrlichiosis in dogs (JW Nesbitt 1981 Department of Pathology, Faculty of Veterinary Science, personal communication) used in experimental studies reported elsewhere.

No definite recommendations can be made as to the treatment of severe chronic cases with canine ehrlichiosis. Since completion of this study 2 more severely leukopaenic German Shepherds have been cured with levamisole-therapy and it is suggested that levamisole should be used as follows:

(i) at a daily oral dosage route of 3-10 mg/kg and
(ii) for not less than 60 days.

When using the drug for any length of time, the possibility of aggravating the leukopaenic state should, however, be kept in mind. A reversible granulocytopenia has been described in man. The use of immuno-stimulants such as levamisole should be investigated further.

In conclusion, it can be stated that dogs were presented with clinical signs of canine ehrlichiosis in all months of the year. A variety of breeds were presented but the German Shepherd breed was especially well represented. A high percentage of German Shepherd Dogs developed the chronic phase of the disease and died. The clinical signs of the disease were found to be mainly non-specific. The terms acute, subacute and chronic are proposed to describe the different stages of the disease. A total white cell count determination was found to be of prognostic value.