Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
www.entomoljournal.com
JEZS 2020; 8(2): 1849-1852

Received: 10-01-2020
Accepted: 12-02-2020

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Canine ehrlichiosis: A review

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Abstract
Ehrlichiosis is a globally distributed canine vector borne disease transmitted by ticks, caused by the rickettsial bacteria *Ehrlichia* spp. Ehrlichiosis affects dogs and humans as well as other domestic and wild animal species. *Ehrlichia* spp. is gram-negative obligate intracellular bacteria with tropism for hematopoietic cells. Three different *Ehrlichia* species can cause canine ehrlichiosis namely *E. canis*, *E. chaffeensis* and *E. ewingii*. In acute cases, fever reticuloendothelial hyperplasia, generalized lymphoadenopathy, splenomegaly and thrombocytopenia are noticed. In chronic infections is characterized by marked splenomegaly, glomerulonephritis and renal failure, meningitis with associated cerebellar ataxia, depression and paresis. The disease can be diagnosed on the basis of clinical signs and can be confirmed by demonstration of the organisms (as clusters or colonies) within the cytoplasm of the mononuclear cells. Tetracyclines are the treatment of choice for rickettsial diseases. For canine ehrlichiosis, tetracycline (22 mg/kg given three times a day for 21 days.) or doxycyclines (5 mg/kg twice a day for 21 days) are recommended. The measures to be taken for this purpose include effective tick control and chemoprophylaxis of dogs in endemic area.

Keywords: Ehrlichiosis, canine, thrombocytopenia, tetracycline and vector borne

Introduction
In the past, a number of obligate intracellular organisms that infect eukaryotic cells were classified in the genus *Ehrlichia* on morphologic and ecologic grounds, however with newer genetic analyses, these organisms has been reclassified in to genera of *Ehrlichia*, *Anaplasma* and *Neorickettsia* all of which are in the family Anaplasmataceae [1]. Ehrlichiosis in dogs also known as canine rickettsiosis, canine hemorrhagic fever, canine tick typhus, tracker dog disease, nairobi bleeding disoreders and tropical canine pancytopenia [2]. It is caused by the *Ehrlichia spp.* Disease is clinically characterized by fever, anorexia, lymphoadenopathy and acute reduction in cellular blood elements, most often thrombocytopenia. Co-infections of *Ehrlichia* with *Anaplasma*, *Rickettsia*, *Babesia* or *Bartonella* spp. Occur frequently as dogs are naturally exposed to multiple tick-borne pathogens. Acute, latent and chronic forms of the disease are recognized, with the latter usually accompanied by severe haematological and bone marrow dysfunctions [3]. As thrombocytopenia is relatively a constant feature of ehrlichiosis, a platlet count is an important screening test. Furthermore, clinical diagnosis may be confirmed by demonstrating the organisms inside leucocytes or platelets, seen as intracytoplasmic inclusion bodies called morulae. In general, ehrlichiosis is diagnosed on basis of combinations of clinical signs, positive serum indirect fluorescent antibody (IFA) titer and response to treatment. In addition PCR has been used to detect and identify *Ehrlichia* and *Anaplsma* species in infected human as well as animals. Moreover, PCR can be used to detect the effictiveness of treatment in in clearing infection. Doxycyclin, oxytetracyclin and imidocarb can be used to treat the infected dogs. Supportive therapy may be necessary to combat wasting and specific organ dysfunction; platelet or whole blood transfusion is needed in case of extensive hemorrhage. Concurrent broad spectrum antibiotics may be given in dogs with severe leucopenia. Ehrlichiosis can be prevented by controlling ticks on dogs.

Etiology
Ehrlichiosis in dog caused by *E. canis*, *E. chaffeensis*, *E. ewingii* and potentially *E. ruminatum* [4]. The organisms are considered as leukocytophilic bacteria and they multiply within the cytoplasmic vacules of circulating monocyte and tissue macrophages [5].

Epidemiology
The diseases is transmitted by the brown dog tick *Rhipicephalus sanguineus* and presents

worldwide distribution [6] but are more prevalent in tropical and subtropical climate. The disease has been reported from India in 1982 [7]. The ticks can transmit the disease for up to 5 months after engorgement. The infection can also be transmitted through blood transfusions. The acute cases occurs mostly in summer because of the greatest activity of the tick vector during that period [8]. German Shepherd Dogs are thought to be susceptible to a particularly severe form of the disease due to inadequate immunogenic response other breeds generally have milder clinical signs.

Table 1: Summary of Ehrlichia pathogens and ehrlichial diseases [9]

Species	Common name of disease(s)	Common natural host(s)	Cells most commonly infected	Primary vector(s)	Distribution
E. canis	Canine monocytic ehrlichiosis (CME)	Dogs and other members of the family Canidae, cats, humans	Primarily mono - nuclear cells (monocytes and lymphocytes)	*Rhipicephalus sanguineus*, *Dermacentor Variabilis*	Worldwide, primarily tropical, subtropical, and temperate climates
E. chaffeensis	Human monocytic ehrlichiosis (HME)	Humans, deer, horses, rodents	Monocytes, macrophages	*Amblyomma americanum*, *Dermacentor Variabilis*	USA, Europe, Africa, South and Central America, Korea
E. ewingii	Canine granulocytic ehrlichiosis (CGE), human granulocytic ehrlichiosis (HGE)	Dogs, humans	Primarily neutrophils and eosinophils	*Amblyomma americanum*, *Otobius megnini*	USA, Africa, Korea
E. muris	Not currently associated with disease	Rodents, Humans	Mononuclear Cells	*Haemaphysalis* spp.	Japan
E. ruminantium	Heartwater disease	Ruminants	Endothelial Cells	*Amblyomma* spp.	Africa, Caribbean

Pathogenesis

On entry organisms invade the monocyte, macrophages and epithelial cells. Monocytes multiply in numbers and entire cytoplasm is filled with them, resulting into destruction of leukocytes and thrombocytes. The severe chronic form is attributed as tropical canine pancytopenia. There is impairment in the production of blood cells. Thrombocytopenia is the most consistent blood abnormality. The causes for such reduction of platelets have been put forth as increased platelets consumptions as a result of inflammatory changes in blood vessels endothelium, increased splenic sequestrations of platelets and immunologic destructions of platelets [10]. In this case, dogs may collapse due to haemorrhage or secondary infections.

Clinical finding

Clinical signs and the severity of illness seen with ehrlichiosis depend on the species of *Ehrlichia* involved and the immune response of the dog. Canine monocytic ehrlichiosis is characterized by three stages, acute, subclinical and chronic but these can be difficult to definitively distinguish in practice.

1) Acute phase

Acute disease lasts between 3 to 5 weeks with clinical findings of fever, anorexia, depression, lymphoadenopathy [11], and splenomegaly. In addition, ocular discharge, pale mucous membranes, hemorrhagic tendencies, or neurological signs. Moreover, bleeding tendencies namely epistaxis, malena, haemetemesis, petechial and ecchymotic haemorrhages on oral gums and ventral abdomen are attributed to thrombocytopenia and damage to vascular endothelium due deposition of immune complexes on the vascular wall [12], oedematous tendencies (ascites) are due to hypoproteinemia [13] or hypoalbuminemia and vasculitis [14, 15], uraemia [16] ; icterus, ascites and lameness [17]. The most commonly observed hemato -logical abnormalities are thrombocytopenia and anemia [10, 18, 19].

2) Subclinical phase

A long-term subclinical phase usually follows the subsidence of clinical signs and can last for several years [20]. Dogs that are unable to eliminate the infectious agent develop subclinical persistent infections and become asymptomatic carriers.

3) Chronic phase

Some infected dog progress to a chronic phase, which can be mild or severe. This is characterized by recurrent clinical and hematological signs including thrombocytopenia, anemia, and pancytopaenia. Dogs may have weight loss, depression, petechiae, pale mucous membranes, edema, and lymphoadenopathy among other signs. In severe cases, the response to antibiotic therapy is poor and dogs often die from massive hemorrhage, severe debilitation, or secondary infections. It is very likely that *E. canis* causes immunosuppressant but currently little is known about the immunobiology of this infection. A recent study in dogs was unable to demonstrate a marked immunosuppressant [21].

Diagnosis

The disease can be diagnosed on the basis of clinical signs and can be confirmed by demonstration of the organisms (as clusters or colonies) within the cytoplasm of the mononuclear cells. They are minute gram negative cocci and stain dark blue to purple with romanovsky stains. The acridine orange stained smears show yellow colored morula stage. The organism can also isolated by *in vitro* cultivations in cell culture [8]. Thrombocytopenia, anaemia and leukopenia are usually the most common hematological abnormalities in canine monocytic ehrlichiosis. Thrombocytopenia is considered as the most common haematological abnormality in dogs either naturally or experimentally infected with *Ehrlichia canis* [22]. Thrombocytopenia may be the result of the decrease of half-life of circulating platelets, endothelium dysfunction and thrombocytes aggregation, increased platelet sequestration in the spleen, and formation of auto-antibodies against platelets [23]. Another possible explanation could be related to variations in virulence of the various strains of *Ehrlichia canis* and antigen heterogeneity [3]. Anaemia is also a common clinical pathology abnormality in canine ehrlichiosis [22]. Various serological test, like indirect immunofluroscence antibody and ELISA have been suggested since many time detection of the organisms in peripheral blood cell is not possible. PCR is a rapid and sensitive test. The hypoalbuminemia, hyperglobulinemia and hypogamma-

globulinemia are the feature of ehrlichiosis.

Differential diagnosis

Anaplasmosis, canine Rocky Mountain spotted fever (another rickettsiosis), babesiosis, bartonellosis, hepatozoonosis, and canine distemper should all be considered as possible differential diagnoses for ehrlichiosis. Molecular characterization by PCR and sequencing may be required to finally determine the specific pathogen involved. Autoimmune-mediated thrombocytopenia, systemic lupus erythematosus or neoplasia (lymphoma or multiple myeloma) should also be considered.

Prognosis

The prognosis is good for dogs with acute ehrlichiosis. For dogs that have reached the chronic stage of the disease, the prognosis is guarded [24]. When bone marrow suppression occurs and there are low levels of blood cells, the animal may not respond to treatment.

Line of treatment

Tetracyclines are the treatment of choice for rickettsial diseases. For canine ehrlichiosis, tetracycline (22 mg/kg given three times a day for 21 days.) or doxycyclines (5 mg/kg twice a day for 21 days) are recommended [4]. Hypoabuminemia in the dog seemed to accelerate the uptake of tetracycline into the red blood cells (Jim and Jerry, 2001) [25]. Most dogs recover from the acute and subclinical phases when treated with doxycycline or other tetracyclines at appropriate dosages for an adequate period of time [26] but many clinicians are now using doxycycline to treat ehrlichiosis in dogs due to better penetration and higher concentration of the drug within the cell [25]. Few researchers suggested that imidocarb dipropionate can be used as first line of treatment against canine ehrlichiosis [27, 28, 29, 2]. Imidocarb dipropionate act by blocking entry of inositol (an essential nutrients) into the infected cell containing parasite thus results in starvation and inhibition of infection [30]. Moreover, available reports suggest that immunological mechanism might be involve in pathogenesis of the disease hence use of immunosuppressive doses of prednisolone has been advocated [2] with other therapy. Papaya (*Carica papaya*) leaf extract (Caripill) can be used as thrumbocyte enhancer as thrumbocytopenia is one of the major haematological changes in canine ehrlichiosis [31, 32, 33]. Supportive therapy must be provided to animals that have clinical signs. Subcutaneous or intravenous fluids are given to dehydrated animals, and severely anemic dogs may require haematinics or blood transfusion.

Zoonotic importance

The first human infection with *E. chaffeensis* was diagnosed in 1986 raising the awareness of *Ehrlichia* spp. as zoonotic pathogens [34]. To date, there is no evidence of direct transmission of *Ehrlichia* spp. from dogs to humans [35] and dogs have not been established as a reservoir for human infection. Moreover, the Brown Dog tick would not appear to be the main vector or reservoir involved in zoonotic transmission because it rarely bites humans [36]. The diseases in man infests in three forms (Chakrabarti, 2012):

1) **Sennetsu Ehrlichiosis:** The disease manifest as acute febrile illness, lymphoadenopathy along with lethargy.
2) **Human Monocytic Ehrlichiosis:** The disease is ascribed as non specific febrile conditions. In addition to fever headache is common. A severe complication which may results is fatal renal failure and encephalopathy**.**
3) **Human Granulocytic Ehrlichiosis:** It was first reported in U.S.A. Disease is clinically characterized by febrile illness, headache and myalgia.

Prevention and control

There are no vaccines currently available to protect dogs from *Ehrlichia* spp. infections. The best means of preventing canine ehrlichiosis is by avoiding exposure to the tick vector. Treatments with ectoparasiticides that repel and kill ticks reduce the risk of disease transmission. Tick control is the most effective method of prevention, but tetracycline at a lower dose can be given daily for 200 days during the tick season in endemic regions.

Conclusion

Anaemia, thrumbocytopenia, lymphadenopathy, pyrexia are important feature of the canine ehrlichiosis. The diasease can be treated with doxycycline, oxytetracycline, imidocarb propionate along with broad spectrum antibiotics, thrumbocyte enhancer and fluid therapy; while in severe cases blood transfusion is required. The infection can be prevented by controlling ticks on dogs. The disease can be managed well with suitable therapeutic regimens, if diagnosed and treated promptly at appropriate stage of infection.

Conflict of interest

The authors declare no conflict of interest with this manuscript.

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