Microbial Pathogenesis 119 (2018) 1–8

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

Equine Granulocytic Anaplasmosis 28 years later

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ARTICLE INFO

Keywords:
Equine granulocytic anaplasmosis
Anaplasma phagocytophilum
Prevalence
Epidemiology

ABSTRACT

Equine granulocytic anaplasmosis (EGA) is an important tick borne disease of equines that is caused by *Anaplasma phagocytophilum (A. phagocytophilum)*. The etiological agent has veterinary as well as public health importance because of its zoonotic nature. *A. phagocytophilum* causes an acute illness in equines with loss of appetite, lethargy, hemorrhages and lameness. Clinically, EGA is diagnosed upon examination of morulae within neutrophils especially granulocytes in the blood. The best diagnostic tool for the detection of EGA is Polymerase chain reaction (PCR). Previous studies suggested that EGA is a self-limiting disease and tetracycline therapy is considered as a best treatment regimen. There is no comprehensive summary on the occurrence and distribution of the infection at global level. Therefore, we intended to provide a comprehensive summary on the prevalence and epidemiology of EGA in different areas of the world. It includes mapping the global distribution of EGA in different areas of the world to identify the endemic regions which may be a source of potential disease outbreak. For this purpose, the published data from 1990 to 2018 on EGA was reviewed and collected by electronic literature search of five databases including Google, Google Scholar, Science Direct, PubMed and Web of Science.

1. Introduction

Arthropod borne diseases are observed to be increasing worldwide in human beings and domestic animals as ticks along with mosquitoes are playing a very important role in transmitting diseases [1]. Infectious diseases may cause serious disaster for animal health and productivity in developing countries [2–11]. Drastic climatic changes along with socio-economic changes have allowed ticks to extend their spatial and temporal distribution. Therefore, the host range of ticks has widened, which result in seasonal transmission of tick borne pathogens (TBPs) [12,13].

Frequent outdoor activity of equines make them prone to tick bites and therefore, result in infection with TBPs [14]. Additionally, the geographical distribution of infected equines and ticks play a very important role in disease transmission in equines throughout the world [13]. In several countries, the epidemiology of tick borne diseases (TBDs) in equines has been described [15–19]. Ticks are responsible for equine piroplasmosis (EP) caused by *Babesia caballi* and *Theileria equi* [15,20–24]. Lyme borreliosis (LB) caused by *Borrelia burgdorferi* and EGA caused by *A. phagocytophilum* [20,25–28].

Anaplasma is originated from the Greek word'*an'*, which means 'without', and '*plasma*-anything molded or formed', the bacterium *A. phagocytophilum* is a rickettsial pathogen having medical and veterinary importance. In the early 1930s this bacterium was described as *Rickettsia phagocytophila* infecting sheep. *Ehrlichia equi*, *Ehrlichia phagocytophila* and the agent of human granulocytic ehrlichiosis are now renamed as *A. phagocytophilum* following the reorganization of *Anaplasmataceae* and *Rickettsiaceae* families in the order *Rickettsiales* [29,30].

EGA is a disease of equines associated with thrombocytopenia [28,31], caused by *A. phagocytophilum*. It is a gram-negative, small, pleomorphic or spheroid shaped bacteria which was reported to reside inside of granulocytes primarily in neutrophilic and eosinophilic of infected animals [32,33]. The inclusion bodies consist of coccoid organisms whose diameter is approximately 0.2 μm as well as large granular aggregates called morulae that are approximately 5 μm in size. In Giemsa or Wright Leishman stain they appear as pale bluish-grey to deep blue inclusion bodies under oil-immersion lens [34]. EGA occurs during seasons of tick activity i.e. spring and autumn [35]. The main transmission of this disease is through ticks but there are some reservoir

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https://doi.org/10.1016/j.micpath.2018.04.001
Received 5 March 2018; Received in revised form 30 March 2018; Accepted 3 April 2018
Available online 04 April 2018

hosts like small rodents; white-footed mice, chipmunks and voles [36–38]. Cervids, lizards and birds are proposed to possess this pathogen in them as well [39–41].

The strains of *A. phagocytophilum* are distinct ecologically and have vast host tropisms [42,43]. Humans, sheep, horses and dogs may be extremely infected by some strain of the pathogen, whereas in case of cross-reactivity (cattle are infected with a strain from equine), clinical signs are not observed in cattle. In rodents and sheep chronic disease occurs, whereas in equines and humans an acute self-limiting infection occurs [44].

Zoonotic tick-borne diseases are an increasing health stress [45]. Humans are accidental or 'dead-end' hosts of *A. phagocytophilum* and develop a disease known as human granulocytic anaplasmosis (HGA) [46]. HGA often show nonspecific symptoms such as muscle ache, fatigue, headache, fever, occasionally vomiting and diarrhea, leukopenia, anemia and thrombocytopenia in humans [46,47]. HGA is considered as 3rd most common tick-borne infection in U.S. and Europe, and a very important vector-borne infection in Asia especially China [48].

2. Epidemiology

EGA is an endemic disease which is reported in different parts of the world (See Fig. 1). Prevalence (%) of EGA reported in various animal species from different countries throughout the world ranges from 0.3% to 73% (Table 1).

2.1. Host range and vectors for disease transmission

A. phagocytophilum is a wide spread multi-host pathogen which includes humans, ruminants, equines, canines, birds, roe deer, white-tailed deer and wild mammals [77]. The main vector throughout Europe is *Ixodesricinus* [14]. However, the *A. phagocytophilum* was also detected from *I. persulcatus* from Latvia [78], *Dermacentor reticulatus, Haemaphysalis concinna* from Russia and Serbia [79]. Table 2 shows reported vectors of *A. phagocytophilum* throughout the world. *A. phagocytophilum* causes disease in humans known as HGA [80], in felines as Feline granulocytic anaplasmosis [81], Pasture fever or Tick-borne fever (TBF) in cattle, sheep and goat [82,83], Canine granulocytic anaplasmosis in canines and EGA in equines [84].

2.2. Transmission

Trans-stadial transmission occurs in EGA, which means that larvae and nymphs should feed on infected animals to attain and spread/transmit the bacteria to next life stage. As discussed earlier *A. phagocytophilum* is transmitted by the ticks of genus *Ixodes* [99,100]. *Ixodes pacificus and I. ricinus* are responsible for transmission of disease [36,101]. Egg, larva, nymph and adult are the developmental stages of this genus. Blood meal is required to mature from larva to nymph and then finally adult. *A. phagocytophilum* is seen in three developmental stages except eggs. Therefore, trans-ovarial transmission does not occur in *A. phagocytophilum* [102].

3. Pathogenesis

The pathogenesis of EGA is not clearly understood [34]. The bacterium enters the dermis by tick bite and is thought to spread through lymphatic system or blood. Hematopoietic and lympho-reticular target cells are invaded by the ehrlichia. Replication takes place within the vacuoles of phagocytes. It is not clear whether these ehrlichia directly

Fig. 1. Prevalence of Equine Granulocytic Anaplasmosis reported (1990–2018) in different countries of the world. Different colors in the map indicate different continents. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)